Exploring Post-Translational Arginine Modification Using Chemically Synthesized Methylglyoxal Hydroimidazolones (MG-Hs)

Tina Wang, Rendy Kartika, and David A. Spiegel*

Department of Chemistry, Yale University, 225 Prospect Street, New Haven, CT 06520

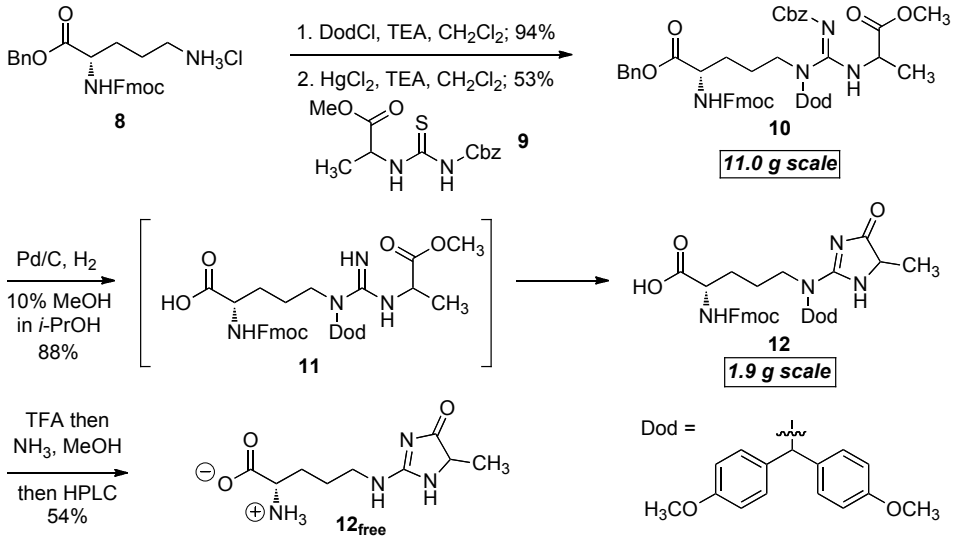
Supporting Information

INDEX

GENERAL EXPERIMENTAL PROCEDURES.

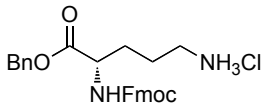
Starting materials were used as received unless otherwise noted. All moisture sensitive reactions were performed in an inert, dry atmosphere of nitrogen in oven dried glassware. Reagent grade solvents were used for extractions and flash chromatography. Reaction progress was checked by analytical thin-layer chromatography (TLC, Merck silica gel 60 F-254 plates). The plates were then monitored with UV illumination followed by visualization with appropriate staining reagents such as anisaldehyde, ninhydrin, or $KMnO_4$. Flash column chromatography was performed using silica gel (230-400 mesh) using Teledyne Isco CombiFlash Rf 200. The solvent compositions reported for all chromatographic separations are on a volume/volume (v/v) basis. Infrared (IR) spectra were recorded on a Thermo Nicolet 6700 FT-IR Spectrometer. Unless otherwise noted, ^{1}H-NMR spectra were recorded on a 500 MHz Bruker spectrometer and are reported in parts per million (ppm) on the δ scale relative to $CDCl_3$ (δ 7.26) as an internal standard. Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, br = broad, m = multiplet), coupling constants (Hz), and integration. Unless otherwise noted, ^{13}C-NMR spectra were recorded on a 125 MHz Bruker spectrometer and are reported in parts per million (ppm) on the δ scale relative to $CDCl_3$ (δ 77.00). LC-MS analyses were performed on a Waters UPLC/MS instrument equipped with a RP-C18 column (1.7 μm particle size, 2.1x50 mm), dual atmospheric pressure chemical ionization (API)/electrospray (ESI) mass spectrometry detector, and photodiode array detector.

MG-H1 SYNTHESIS.



Scheme S1

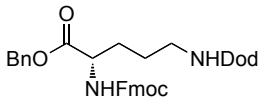
(*S*)-benzyl 2-((((9*H*-fluoren-9-yl)methoxy)carbonyl)amino)-5-aminopentanoate Hydrochloride (8)



8

Esterfication of N^{α}-Fmoc-N^{δ}-Boc-ornithine to the corresponding benzyl ester was performed according using a modified version of an established protocol.[1] Thus, N^{α}-Fmoc-N^{δ}-Boc-ornithine (71.00 g, 156.3 mmol) was added to a flask containing CH_2Cl_2 (1000 mL), and the solution was cooled to 0°C. DMAP (1.91 g, 15.6 mmol) and DIPEA (40.89 mL, 234.5 mmol) were sequentially added, followed by CbzCl (24.54 mL, 171.9 mmol), which was added in 3 portions over 30 minutes. After stirring at 0°C for 5 hours, the mixture was poured into a separatory funnel and washed with 2M aqueous HCl (500 mL). After separating the layers, the organic layer was dried with $MgSO_4$ and filtered. The resulting filtrate was concentrated under vacuum to reduce the volume to 500 mL. 2M HCl in Et_2O (390.8 mL, 781.5 mmol) was then added, and a white precipitate began to form within 10 minutes. After stirring for an additional 24 hours, the solvent was removed under vacuum to give ornithine salt **8** as white solid in 97% yield (72.71 g, 151.2 mmol). This crude material was used in the next step without further purification. HR-MS: $(M+1)^+$ = 445.2127 (experimental); exact mass = 445.2127 (theoretical) for $C_{27}H_{29}N_2O_4$.

(*S*)-benzyl 2-((((9*H*-fluoren-9-yl)methoxy)carbonyl)amino)-5-((bis(4-methoxyphenyl) methyl)amino)pentanoate (S1)



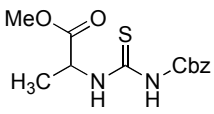
S1

Bis(4-methoxyphenyl)methanol (DodOH, 8.00 g, 32.7 mmol) was added to a flask containing Et_2O (200 mL), and the solution was cooled to 0°C. 12M aqueous HCl (16.3 mL, 196 mmol) was then added dropwise, which caused the solution to turn slightly pink. The heterogeneous reaction mixture was allowed to warm to room temperature, stirred vigorously for 30 minutes, and then poured into a separatory funnel. After separation of layers, the organic layer was dried with 1:1 mixture of $MgSO_4$ and $NaHCO_3$. The solids were then filtered to give DodCl in Et_2O solution, which was immediately used in the next step without further purification.

Finely powdered ornithine-derived hydrochloride salt **8** (12.10 g, 25.16 mmol) was added to a flask containing CH_2Cl_2 (500 mL). After cooling the suspension to 0°C, Et_3N (17.5 mL, 125.7 mmol) was added. The freshly prepared DodCl solution described above was then added dropwise over 30 minutes, which caused the solution to become clear. The reaction mixture was allowed to warm to room temperature, stirred for an additional 2 hours, and then concentrated under vacuum to afford a yellow oil. Purification was performed in 2 batches using an automated organic purification system (Teledyne Iso, Inc.) on a normal-phase 120 g Redi*Sep*® column as the stationary phase. CH_2Cl_2 and EtOAc were used as the mobile phase. Column conditions: 100% CH_2Cl_2 for 1 column volume followed by 0 → 50% EtOAc over 15 column volumes. Fully protected ornithine derivative **S1** was isolated in 94% yield (15.89 g, 23.69 mmol) as a thick yellow oil possessing the following spectral characteristics: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.77 (d, *J* = 7.3, 2H), 7.60 (d, *J* = 7.4, 2H), 7.44 – 7.24 (m, 13H), 6.82 (d, *J* = 2.6, 2H), 6.81 (d, *J* = 2.6, 2H), 5.93 (d, *J* = 8.1, 1H), 5.22 (d, *J* = 12.2, 1H), 5.16 (d, *J* = 12.2, 1H), 4.69 (s, 1H), 4.48 – 4.37 (m, 4H), 4.23 (t, *J* = 7.0, 1H), 3.75 (s, 6H), 2.55 (b, 2H), 1.92 (m, 1H), 1.83 (m, 1H), 1.57 – 1.45 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 172.34, 158.47, 155.97, 143.93, 143.77, 141.25,

141.24, 136.49, 136.47, 135.33, 128.58, 128.41, 128.25, 128.14, 128.10, 127.64, 127.03, 125.09, 119.91, 113.79, 67.05, 66.98, 66.22, 55.17, 53.83, 47.45, 47.17, 30.50, 25.74. IR *f* (cm^{-1}) = 3337, 3034, 2951, 2834, 1720, 1507, 1243, 1032. HR-MS: $(M+1)^+$ = 671.3131 (experimental); exact mass = 671.3121 (theoretical) for $C_{42}H_{43}N_2O_6$. $[\alpha]^{23}_D$ = -2.15 (c = 5.3 $CHCl_3$).

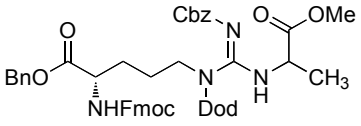
(*S*)-Methyl 2-(3-((benzyloxy)carbonyl)thioureido)propanoate (9)



9

CbzNCS[2] (11.60 g, 60.04 mmol) was added to a flask containing CH_2Cl_2 (300 mL), followed by L-alanine-OMe•HCl (7.00 g, 50.14 mmol). After cooling the suspension to 0°C, Et_3N (35.0 mL, 251.3 mmol) was added dropwise, which caused the mixture to become clear. The reaction was further stirred for 2 hours at room temperature, then concentrated under vacuum to afford a yellow paste. This residue was re-dissolved in CH_2Cl_2 (300 mL), then washed with 2M aqueous HCl (100 mL). After separation of layers, the organic layer was dried over $MgSO_4$, filtered, and concentrated under vacuum to give crude material as yellow oil. using an automated organic purification system (Teledyne Iso, Inc.) and a normal-phase 120 g Redi*Sep*® column as the stationary phase. Hexanes and EtOAc were used as the mobile phase. Column conditions: 100% hexanes for 1 column volume followed by 0 → 30% EtOAc over 15 column volumes. Thiourea **9** was isolated in 95% yield (14.12 g, 47.65 mmol) as an amorphous yellow solid possessing the following spectral characteristics: ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.12 (d, *J* = 6.4, 1H), 8.49 (s, 1H), 7.46 – 7.28 (m, 5H), 5.20 (d, *J* = 12.2, 1H), 5.17 (d, *J* = 12.1, 1H), 5.01 (p, *J* = 7.1, 1H), 3.77 (s, 3H), 1.54 (d, *J* = 7.2, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 178.73, 172.11, 152.33, 134.40, 128.69, 128.59, 128.23, 68.10, 53.59, 52.54, 17.44. IR *f* (cm^{-1}) = 3284, 3239, 3032, 2952, 1718, 1506, 1189, 1069. HR-MS: $(M+1)^+$ = 297.0898 (experimental); exact mass = 297.0909 (theoretical) for $C_{13}H_{17}N_2O_4S$. $[\alpha]^{23}_D$ = +21.8 (c = 7.5 $CHCl_3$).

(5*S*,12*S*,*Z*)-methyl 5-((benzyloxy)carbonyl)-10-(((benzyloxy)carbonyl)imino)-9-(bis(4-methoxyphenyl)methyl)-1-(9*H*-fluoren-9-yl)-12-methyl-3-oxo-2-oxa-4,9,11-triazatridecan-13-oate (10)

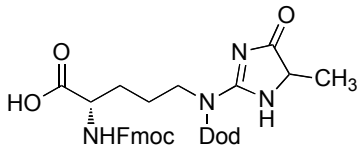


10

Ornithine derivative **S1** (15.00 g, 22.36 mmol) was dissolved in CH_2Cl_2 (500 mL). After cooling the solution to 0°C, thiourea **9** (7.29 g, 24.60 mmol), Et_3N (15.57 mL, 111.8 mmol), and $HgCl_2$ (7.28 g, 6.83 mmol) were added sequentially. Within 5 minutes, a yellow precipitate began to form, and the reaction was allowed to warm to room temperature. After stirring for 2 hours, the yellow precipitate was then filtered through a pad of celite and then washed with CH_2Cl_2 (2x100 mL). The filtrate was concentrated under vacuum to give crude material as yellow solid. Purification was performed in 2 batches using Teledyne Isco with a normal phase 120 g Redi*Sep* column as the stationary phase. Hexanes and EtOAc were used as the mobile phase. Column conditions: 100% hexanes for 1 column volume followed by 50 → 100% EtOAc over 15 column volumes. Fully protected carboxyethylarginine **10** was isolated in 53% yield (11.08 g, 11.87 mmol) as an amorphous white solid possessing the following spectral characteristics: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.76 (d, *J* = 7.4, 2H), 7.58 (d, *J* = 7.3, 2H), 7.43 – 7.18 (m, 14H), 7.14 (d, *J* = 8.4, 2H), 7.08 (d, *J* = 8.5, 2H), 6.83 (t, *J* = 9.4, 4H), 6.40 (s, 1H), 6.29 (s, 1H), 5.45 (d, *J* = 8.0, 1H), 5.20 – 4.99 (m, 4H), 4.44 – 4.29 (m, 3H), 4.25 (m, 1H), 4.17 (t, *J* = 7.0, 1H), 3.77 (s, 3H), 3.75 (s, 3H), 3.61 (s, 3H), 3.32 (m, 1H), 3.21 (m, 1H), 1.55 – 1.40 (m,

3H), 1.26 (b, 1H), 1.26 (d, J = 6.9, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 173.39, 171.80, 160.26, 159.18, 159.14, 159.09, 156.06, 143.82, 143.74, 141.20, 137.95, 135.18, 130.59, 130.40, 129.76, 129.71, 128.56, 128.39, 128.18, 128.14, 127.88, 127.65, 127.36, 127.04, 127.03, 125.13, 125.09, 119.89, 114.01, 113.97, 67.11, 66.68, 64.88, 55.20, 53.24, 52.35, 51.67, 47.03, 46.45, 29.87, 23.75, 18.31. IR f (cm^{-1}) = 3368, 3066, 2953, 2837, 1721, 1509, 1247, 905, 724. HR-MS: $(M+1)^+$ = 933.4029 (experimental); exact mass = 933.4075 (theoretical) for $C_{55}H_{57}N_4O_{10}$. $[\alpha]^{23}_D$ = -13.56 (c = 5.0 $CHCl_3$).

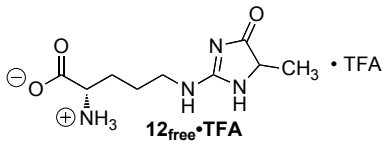
(*S*)-2-((((9*H*-fluoren-9-yl)methoxy)carbonyl)amino)-5-((bis(4-methoxyphenyl) methyl)((*S*)-5-methyl-4-oxo-4,5-dihydro-1*H*-imidazol-2-yl)amino)pentanoic acid (12)



12

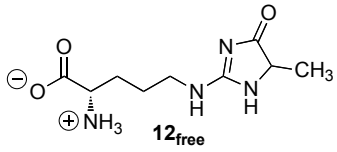
10% Pd/C (3.32 g, 3.12 mmol) was added to a flask containing fully protected carboxyethylarginine (**10**, 2.91 g, 3.12 mmol). After purging the system with N_2 for 5 minutes, a degassed solvent mixture consisting of 10% MeOH in iPrOH (400 mL) was then carefully added. A gentle stream of H_2 was then bubbled into the black suspension for one hour, and the reaction was stirred under H_2 balloon atmosphere for 24 hours. At this point, LC-MS indicated a mixture of unreacted starting material **10**, monodebenzylation product, and **11**. An additional 10% Pd/C (2.91 g, 3.12 mmol) as a suspension in 10% MeOH in iPrOH (100 mL) was then added via syringe, and the reaction was further stirred for 24 hours. At this point, LC-MS indicated a complete reaction and only **12** was detected. After re-purging the system with N_2 with 5 minutes, the black solid was filtered over a thick pad of celite and washed with MeOH (1500 mL). The solvent was then removed under vacuum to give Fmoc-(MG-H1)-Dod **12** in 88% yield (1.86 g, 2.75 mmol) as gray solid. The crude material was used in peptide synthesis without further purification. For characterization purposes, a small aliquot of crude material was purified using preparatory HPLC with a SunFire Prep C18 OBD 10 mm 19x150 mm reverse-phase column as the stationary phase. H_2O and MeCN both buffered with 0.1% formic acid were used as the mobile phase. HPLC conditions: UV collection 265 nm, flow rate 20 mL/min, 10% MeCN for 5 minutes followed by 10% → 60% MeCN linear gradient over 30 minutes. The HPLC fractions were combined and lyophilized to give **12** as a formate salt possessing the following spectral characteristics: ^{1}H NMR (500 MHz, DMSO) δ 12.60 (b, 1H), 8.15 (s, 1H), 7.89 (d, J = 7.5, 2H), 7.70 (d, J = 7.5, 2H), 7.41 (t, J = 7.4, 3H), 7.31 (dd, J = 7.3, 12.5, 2H), 7.06 (d, J = 5.5, 2H), 7.05 (d, J = 6.0, 2H), 6.93 – 6.89 (m, 5H), 4.23 (m, 3H), 3.87 (m, 1H), 3.73 (s, 3H), 3.71 (s, 3H), 3.63 (s, 1H), 3.30 (b, 2H), 1.41 (b, 1H), 1.30 (b, 1H), 1.21 (d, J = 6.6, 3H), 1.06 (s, 1H), 0.94 (s, 1H). ^{13}C NMR (126 MHz, DMSO) δ 188.91, 173.56, 170.36, 163.04, 158.64, 158.61, 155.92, 143.79, 143.77, 140.69, 140.67, 130.81, 129.64, 129.45, 127.62, 127.04, 127.02, 125.26, 120.07, 113.94, 113.89, 65.63, 56.62, 55.06, 55.03, 53.48, 46.60, 27.90, 24.58 (b), 17.73. IR f (cm^{-1}) = 3251, 3010, 2960, 1704, 1658, 1570, 1247, 1030, 739. HR-MS: $(M+1)^+$ = 677.2971 (experimental); exact mass = 677.2975 (theoretical) for $C_{39}H_{41}N_4O_7$. $[\alpha]^{23}_D$ = +5.65 (c = 1.1 $CHCl_3$).

(2S)-2-amino-5-((5-methyl-4-oxo-4,5-dihydro-1H-imidazol-2-yl)amino)pentanoic acid (12_{free})



12$_{free}$•TFA

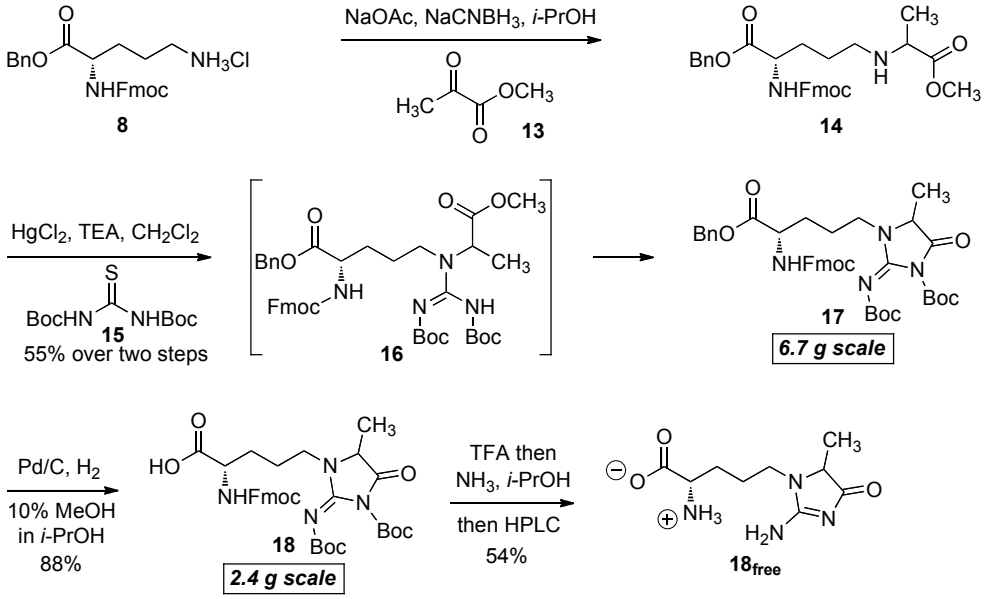
TFA (50 mL) was added to a flask containing Fmoc-(MG-H1)-Dod (**12**, 1.17 g, 1.73 mmol). The reaction was stirred at room temperature for 24 hours, whereupon the solvent was removed under vacuum to give a yellow oil. To this was added 7 M NH_3 in MeOH (20 mL), and the reaction was stirred at room temperature for 24 hours. The solvent was removed under vacuum, and the residue was dissolved in H_2O (10 mL) and washed with CH_2Cl_2 (2 x 10 mL). Purification was preformed using preparatory HPLC with a SunFire Prep C18 OBD 10 mm 19x150 mm reverse-phase column as the stationary phase. H_2O and MeCN both buffered with 0.1% formic acid were used as the mobile phase. HPLC conditions: UV collection 214 nm, flow rate 20 mL/min, 0% MeCN for 5 minutes followed by 0% → 100% MeCN linear gradient over 2 minutes. The HPLC fractions were combined and lyophilized to give free MG-H1, an amorphous white solid, as a formate salt in 54% yield (183 mg, 2.69 mmol). Dissolution of this material in TFA (0.1% in H_2O) followed by lyophilization quantitatively provided the corresponding TFA salt (**12$_{free}$•TFA**), which was found to possess the following spectral characteristics: ^{1}H NMR (400MHz, D_2O) δ 4.48 – 4.38 (m, 1H), 3.96 (t, *J* = 6.0, 1H), 3.41 (t, *J* = 7.2, 2H), 2.06 – 1.92 (m, 2H), 1.88 – 1.69 (m, 2H), 1.48 (d, *J* = 6.8, 2H), 1.45 (d, *J* = 7.2, 1H). ^{13}C NMR (101 MHz, D_2O) δ 177.88, 177.23, 174.73, 172.42, 163.23, 162.95, 162.67, 162.39, 156.95, 155.81, 119.84, 117.52, 115.20, 112.87, 55.59, 55.10, 52.99, 42.48, 41.43, 40.50, 27.05, 26.89, 24.23, 23.67, 23.45, 15.46, 15.33. IR *f* (cm^{-1}) = 3028, 1783, 1708, 1672, 1432, 1289, 1200, 1137, 840, 799, 723. HR-MS $(M+1)^+$ = 229.1292 (experimental); exact mass = 229.1295 (theoretical) for $C_9H_{16}N_4O_3$.



12$_{free}$

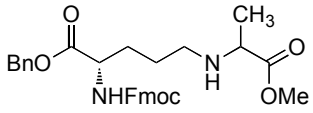
The TFA salt (**12$_{free}$•TFA**) was then quantitatively converted into the free base (**12$_{free}$**) by titration with KOD. This material was found to possess the following spectral characteristics: ^{1}H NMR (400MHz, D_2O pH 7.05) δ 4.15 (m, 1H), 3.76 (t, *J* = 6.0, 1H), 3.37 (m, 1H), 3.30 (m, 1H), 1.96-1.85 (m, 2H), 1.82 – 1.57 (m, 2H), 1.34 (m, 3H).

MG-H2 SYNTHESIS.



Scheme S2

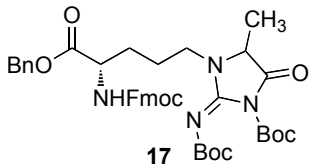
(2*S*)-benzyl 2-((((9*H*-fluoren-9-yl)methoxy)carbonyl)amino)-5-((1-methoxy-1-oxopropan-2-yl)amino)pentanoate (14)



14

Finely powdered ornithine-derivative **8** (8.00 g, 16.63 mmol) was added to a flask containing isopropanol (400 mL). Methyl pyruvate (7.67 mL, 83.15 mmol), NaOAc (6.82 g, 83.15 mmol), and $NaCNBH_3$ (6.27 g, 99.78 mmol). This suspension was stirred overnight at room temperature and then concentrated under vacuum to give a white pasty residue, which was subsequently partitioned with a 1:1 mixture of CH_2Cl_2 and saturated $NaHCO_3$ aqueous solution. After separation of layers in a separatory funnel, the aqueous layer was extracted with CH_2Cl_2 (2x100 mL). The organic layers were then combined, dried over $MgSO_4$, filtered, and concentrated under vacuum to give crude **14** as yellow oil (11.57 g) and used in the next step without further purification. For characterization purposes, a small aliquot of crude material was purified using Teledyne Isco with a normal phase 40 g Redi*Sep* column as the stationary phase. Hexanes and EtOAc were used as the mobile phase. Column conditions: 100% hexanes for 1 column volume followed by 50 → 100% EtOAc over 15 column volumes. Purified material was found to possess the following spectral characteristics: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.76 (d, *J* = 7.5, 2H), 7.60 (d, *J* = 7.3, 2H), 7.40 (t, *J* = 7.4, 2H), 7.32 (dd, *J* = 9.8, 17.3, 7H), 6.29 (d, *J* = 8.0, 0.5H), 6.13 (d, *J* = 7.8, 0.5H), 5.20 (d, *J* = 12.4, 1H), 5.17 (d, *J* = 12.5, 1H), 4.49 – 4.34 (m, 3H), 4.22 (t, *J* = 6.8, 1H), 3.71 (2s, 3H), 3.31 (q, *J* = 7.0, 0.5H), 3.27 (q, J = 6.1, 0.5H), 2.61 (m, 1H), 2.46 (m, 0.5H), 2.40 (m, 0.5H), 1.98 – 1.78 (m, 2H), 1.53 – 1.46 (m, 2H), 1.26 (d, *J* = 6.4, 1.5 Hz), 1.25 (d, *J* = 6.4 Hz, 1.5H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 176.01, 175.97, 172.23, 156.04, 156.01, 143.92, 143.75, 141.23, 141.21, 135.32, 135.30, 128.53, 128.36, 128.20, 127.59, 126.98, 125.01, 119.88, 119.87, 67.00, 66.78, 66.74, 56.45, 56.25, 53.71, 53.65, 51.70, 47.22, 47.14, 47.05, 30.34, 30.11, 25.68, 25.53, 18.97, 18.93. IR *f* (cm^{-1}) = 3327, 3065, 2950, 1716, 1172, 730. HR-MS $(M+1)^+$ = 531.2464 (experimental); exact mass = 531.2495 (theoretical) for $C_{31}H_{36}N_2O_6$. $[\alpha]^{23}_D$ = -3.65 (c = 9.8 $CHCl_3$).

(*Z*)-*tert*-butyl 3-((*S*)-4-((((9*H*-fluoren-9-yl)methoxy)carbonyl)amino)-5-(benzyloxy)-5-oxopentyl)-2-((*tert*-butoxycarbonyl)imino)-4-methyl-5-oxoimidazolidine-1-carboxylate (17)

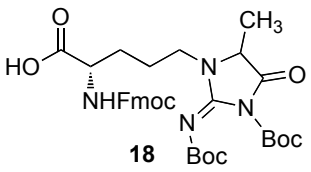


17

Crude amino ester **14** (11.57 g) was dissolved in CH_2Cl_2 (300 mL). After cooling the solution to 0°C, *di*-Boc-thiourea **15** (5.11 g, 18.29 mmol), Et_3N (11.58 mL, 83.15 mmol), and $HgCl_2$ (5.42 g, 19.96 mmol) were added sequentially. Within 5 minutes, a yellow precipitate began to form. The reaction was allowed to warm to room temperature, and the precipitate slowly turned black. After stirring for 2 hours, the black precipitate was then filtered through a pad of celite and then washed with CH_2Cl_2 (2x100 mL). The filtrate was concentrated under vacuum to give crude material as yellow oil. Purification was performed using Teledyne Isco with a normal phase 120 g Redi*Sep* column as the stationary phase. Hexanes and EtOAc were used as the mobile phase. Column conditions: 100% hexanes for 1 column volume followed by 0 → 40% EtOAc over 15 column volumes and then 40%

EtOAc for 4 column volumes. Fully protected MG-H2 **17** was isolated in 55% yield over 2 steps (6.74 g, 9.10 mmol) as an amorphous white solid possessing the following spectral characteristics: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.77 (d, *J* = 7.5, 2H), 7.60 (d, *J* = 6.2, 2H), 7.35 (m, 9H), 5.47 (d, *J* = 8.1, 1H), 5.23 (d, *J* = 12.0, 1H), 5.14 (d, *J* = 12.0, 1H), 4.39 (m, 3H), 4.21 (t, *J* = 6.9, 1H), 3.78 (m, 1H), 3.73 (m, 1H), 3.13 (m, 1H), 1.88 (m, 1H), 1.71 (m, 1H), 1.63 – 1.55 (b, 2H), 1.59 (s, 9H), 1.48 (s, 9H), 1.35 (d, *J* = 6.0, 1.5H), 1.34 (d, *J* = 6.0, 1.5H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.76, 170.28, 170.22, 159.01, 158.98, 155.93, 155.86, 149.84, 146.26, 146.24, 143.79, 143.63, 143.60, 141.27, 135.08, 135.04, 128.68, 128.65, 128.56, 128.53, 127.71, 127.70, 127.05, 125.05, 125.00, 120.00, 119.98, 119.97, 85.94, 85.91, 79.78, 79.76, 67.39, 67.36, 67.05, 54.69, 54.46, 53.46, 53.26, 47.08, 41.43, 41.20, 29.86, 29.69, 28.21, 27.77, 23.09, 22.81, 15.47, 15.38. IR *f* (cm^{-1}) = 3327, 3065, 2980, 2935, 1762, 1624, 1128, 734. HR-MS $(M+1)^+$ = 741.3495 (experimental); exact mass = 741.3500 (theoretical) for $C_{41}H_{49}N_4O_9$. $[\alpha]^{23}_D$ = +0.90 (c = 6.9 $CHCl_3$).

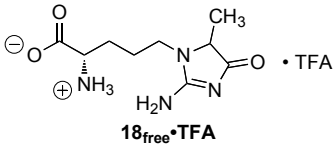
(2*S*)-2-((((9*H*-fluoren-9-yl)methoxy)carbonyl)amino)-5-((*Z*)-3-(*tert*-butoxycarbonyl)-2-((*tert*-butoxycarbonyl)imino)-5-methyl-4-oxoimidazolidin-1-yl)pentanoic acid (18)



18

10% Pd/C (4.51 g, 4.24 mmol) was added to a flask containing fully protected MG-H2 **17** (3.35g, 4.22 mmol). After purging the system with N_2 for 5 minutes, a degassed solvent mixture consisting of 10% MeOH in iPrOH (100 mL) was then carefully added via syringe. A gentle stream of H_2 was then bubbled into the black suspension, and the reaction was stirred for one hour at which starting material was fully consumed. After re-purging the system with N_2 for 5 minutes, the black solid was filtered over a thick pad of celite and washed with MeOH (1500 mL). The solvent was then removed under vacuum to give Fmoc-(MG-H2)-*di*-Boc **18** in 88% yield (2.42 g, 3.72 mmol) as a gray solid. The crude material was used in peptide synthesis without further purification. For characterization purposes, a small aliquot of crude material was purified using Teledyne Isco with a normal phase 40 g Redi*Sep* column as the stationary phase. CH_2Cl_2 and MeOH were used as the mobile phase. Column conditions: 100% CH_2Cl_2 for 1 column volume followed by 0 → 10% MeOH over 15 column volumes. Purified material was found to possess the following spectral characteristics: ^{1}H NMR (500 MHz, DMSO) δ 12.77 (b, 1H), 7.89 (d, *J* = 7.5, 2H), 7.72 (d, *J* = 7.2, 2H), 7.66 (d, *J* = 8.2, 1H), 7.41 (t, *J* = 7.4, 2H), 7.33 (t, *J* = 7.4, 2H), 4.33 (p, *J* = 6.2, 13.7, 1H), 4.31 (m, 2H), 4.22 (t, *J* = 6.9, 1H), 3.95 (m, 1H), 3.58 (m, 1H), 3.19 (m, 1H), 1.78 – 1.52 (m, 4H), 1.49 (s, 9H), 1.37 (s, 9H), 1.35 (d, *J* = 6.8, 3H). ^{13}C NMR (126 MHz, DMSO) δ 173.79, 173.70, 171.01, 170.94, 158.37, 156.18, 156.13, 149.81, 149.76, 146.19, 143.83, 143.77, 143.76, 140.71, 127.61, 127.06, 125.25, 120.09, 84.82, 84.81, 78.03, 78.01, 65.60, 54.81, 54.12, 53.68, 53.67, 46.64, 41.39, 40.74, 27.99, 27.78, 27.41, 23.81, 23.48, 14.95, 14.73. IR *f* (cm^{-1}) = 3319, 2979, 1765, 1712, 1132, 752. HR-MS $(M+1)^+$ = 651.2968 (experimental); exact mass = 651.3030 (theoretical) for $C_{34}H_{43}N_4O_9$. $[\alpha]^{23}_D$ = +16.22 (c = 5.4 $CHCl_3$).

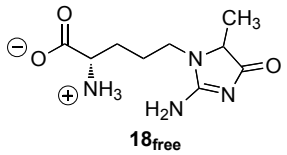
(2S)-2-amino-5-(2-amino-5-methyl-4-oxo-4,5-dihydro-1H-imidazol-1-yl)pentanoic acid (18_{free})



18_{free}•TFA

TFA (5 mL) was added to a flask containing Fmoc-(MG-H2)-*di*-Boc (**18**, 73.9 mg, 114 μmol). The reaction was stirred at room

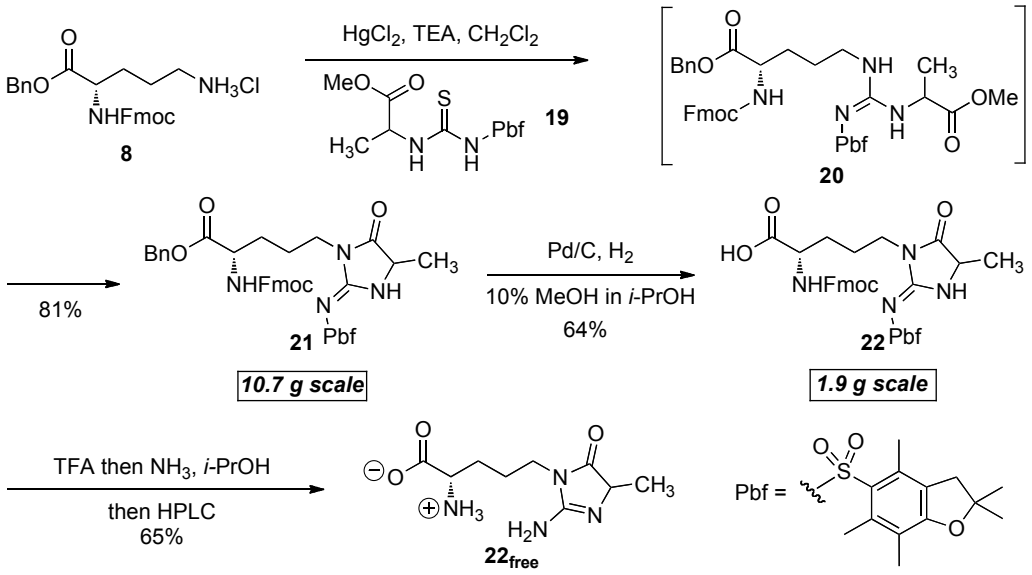
temperature for 2 hours, whereupon the solvent was removed under vacuum to give a yellow oil. To this was added 2 M NH_3 in ^{i}PrOH (10 mL), and the reaction was stirred at room temperature for 24 hours. The solvent was removed under vacuum, and the residue was dissolved in H_2O (2 mL) and washed with CH_2Cl_2 (2 x 2 mL). Purification was preformed using preparatory HPLC with a SunFire Prep C18 OBD 10 mm 19x150 mm reverse-phase column as the stationary phase. H_2O and MeCN both buffered with 0.1% formic acid were used as the mobile phase. HPLC conditions: UV collection 214 nm, flow rate 20 mL/min, 0% MeCN for 5 minutes followed by 0% → 100% MeCN linear gradient over 2 minutes. The HPLC fractions were combined and lyophilized to give free MG-H2, an amorphous white solid, as a formate salt in 65% yield (25.8 mg, 73.7 μmol). Dissolution of this material in TFA (0.1% in H_2O) followed by lyophilization quantitatively provided the corresponding TFA salt (**18_{free}•TFA**), which was found to possess the following spectral characteristics: ^{1}H NMR (400MHz, D_2O) δ 4.43 (q, J = 7.2, 1H), 3.98 (t, J = 6.0, 1H), 3.68-3.44 (m, 2H), 2.06-1.88 (m, 2H), 1.88-1.64 (m, 2H), 1.49 (d, J = 7.2, 3H). ^{13}C NMR (101 MHz, D_2O) δ 178.98, 173.97, 170.16, 162.84, 162.49, 162.14, 161.79, 158.27, 120.50, 117.59, 114.69, 111.79, 67.47, 62.30, 58.77, 53.91, 41.37, 26.97, 25.84, 22.46, 13.51. IR f (cm^{-1}) = 3008, 1781, 1707, 1672, 1543, 1434, 1320, 1198, 1137, 838, 799, 723. HR-MS $(M+1)^{+}$ = 228.1293 (experimental); exact mass = 229.1295 (theoretical) for $C_9H_{16}N_4O_3$.



18_{free}

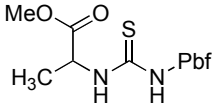
The TFA salt (**18_{free}•TFA**) was then quantitatively converted into the free base (**18_{free}**) by titration with KOD. This material was found to possess the following spectral characteristics: ^{1}H NMR (400MHz, D_2O pH 7.14) δ 4.13 (q, J = 7.2, 1H), 3.76 (m, 2H), 3.55-3.35 (m, 1H), 1.96-1.58 (m, 4H), 1.37 (d, J = 7.2, 3H).

MG-H3 SYNTHESIS.



Scheme S3

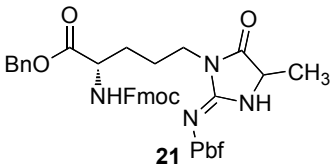
Methyl 2-(3-((2,2,4,6,7-pentamethyl-2,3-dihydrobenzofuran-5-yl)sulfonyl) thioureido)propanoate (19)



19

$PbfNH_2$ (7.00 g, 25.98 mmol) was added to a flask containing THF (300 mL), followed by (*S*)-methyl 2-isothiocyanatopropanoate[3] (4.15 g, 28.58 mmol) and Cs_2CO_3 (9.32 g, 28.61 mmol). The suspension was refluxed overnight and then cooled to 0°C. The reaction mixture was then acidified by a slow addition of 2M aqueous HCl (100 mL) and poured into a separatory funnel. After separation of layers, the aqueous layer was extracted with CH_2Cl_2 (2x100 mL). The organic layers were then combined, dried over $MgSO_4$, filtered, and concentrated under vacuum to give crude material as yellow oil. Purification was performed using Teledyne Isco with a normal phase 120 g Redi*Sep* column as the stationary phase. Hexanes and EtOAc were used as the mobile phase. Column conditions: 100% hexanes for 1 column volume followed by 0 → 60% EtOAc over 15 column volumes. Thiourea **19** was isolated in 93% yield (10.03 g, 24.22 mmol) as an amorphous yellow solid (racemic) possessing the following spectral characteristics: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.35 (d, *J* = 7.0, 1H), 8.26 (s, 1H), 4.86 (p, *J* = 7.1, 1H), 3.72 (s, 3H), 2.98 (s, 2H), 2.60 (s, 3H), 2.54 (s, 3H), 2.11 (s, 3H), 1.47 (s, 6H), 1.37 (d, *J* = 7.1, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 177.60, 172.03, 160.87, 140.14, 134.67, 126.74, 125.74, 118.68, 87.43, 53.79, 52.57, 42.92, 28.44, 19.19, 17.54, 17.49, 12.44. IR *f* (cm^{-1}) = 3315, 2975, 2934, 2933, 1741, 1531, 1447, 1367, 1128, 1090. HR-MS $(M+1)^+$ = 415.1347 (experimental); exact mass = 415.1361 (theoretical) for $C_{18}H_{27}N_2O_5S_2$. $[\alpha]^{23}_D$ = 0.0 (c = 7.5 $CHCl_3$).

(2*S*)-benzyl 2-((((9*H*-fluoren-9-yl)methoxy)carbonyl)amino)-5-((*E*)-4-methyl-5-oxo-2-(((2,2,4,6,7-pentamethyl-2,3-dihydrobenzofuran-5-yl)sulfonyl)imino)imidazolidin-1-yl)pentanoate (21)

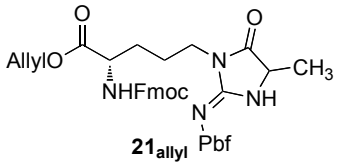


21

Finely powdered ornithine-derivative **8** (8.00 g, 16.63 mmol) was added to a flask containing CH_2Cl_2 (300 mL). After cooling the reaction to 0°C, thiourea **19** (7.58 g, 18.29 mmol), Et_3N (11.6 mL, 83.29 mmol), and $HgCl_2$ (5.42 g, 19.96 mmol) were added sequentially. Within 5 minutes, a yellow precipitate began to form, and the reaction was allowed to warm to room temperature. After stirring for 2 hours, the yellow precipitate was then filtered through a pad of celite and washed with CH_2Cl_2 (2x100 mL). The filtrate was concentrated under vacuum to give crude material as yellow solid. Purification was performed using Teledyne Isco with a normal phase 120 g Redi*Sep* column as the stationary phase. Hexanes and EtOAc were used as the mobile phase. Column conditions: 100% hexanes for 1 column volume followed by 20 → 60% EtOAc over 20 column volumes. Fully protected MG-H3 **21** was isolated in 81% yield (10.69 g, 13.48 mmol) as an amorphous gray solid possessing the following spectral characteristics: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.76 (d, *J* = 7.4, 2H), 7.65 (s, 1H), 7.59 (d, *J* = 7.0, 2H), 7.39 (t, *J* = 7.2, 2H), 7.34 – 7.28 (m, 7H), 5.39 (s, 1H), 5.11 (s, 1H), 5.08 (d, *J* = 12.1, 1H), 4.42 – 4.39 (m, 2H), 4.34 (m, 1H), 4.21 (t, *J* = 7.0, 1H), 4.13 (p, *J* = 6.5, 1H), 3.51 (b, 2H), 2.92 (s, 2H), 2.56 (s, 3H), 2.51 (s, 3H), 2.09 (s, 3H), 1.84 (b, 1H), 1.66 – 1.60 (m, 3H), 1.46 – 1.43 (m, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 173.57, 171.79, 159.42, 155.83, 155.00, 154.97, 143.82, 143.70, 141.25, 138.91, 135.06, 132.82, 131.00, 128.61, 128.48, 128.33, 128.32, 127.66, 127.05, 125.09, 124.92, 119.93, 117.79, 86.69, 67.30, 67.10, 53.79, 53.55, 53.51, 47.09, 43.00, 38.88, 38.84, 29.65, 29.58, 28.50, 23.72, 23.65, 19.13, 17.85,

17.36, 12.36. IR *f* (cm^{-1}) = 3347, 3064, 2974, 2938, 1718, 1618, 1264, 1087, 731. HR-MS $(M+1)^+$ = 793.3287 (experimental); exact mass = 793.3271 (theoretical) for $C_{44}H_{49}N_4O_8S$. $[\alpha]^{23}_D$ = +2.89 (c = 15.7 $CHCl_3$).

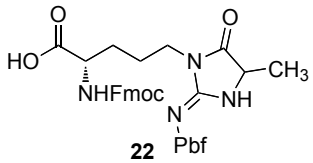
(2*S*)-allyl 2-((((9*H*-fluoren-9-yl)methoxy)carbonyl)amino)-5-((*E*)-4-methyl-5-oxo-2-(((2,2,4,6,7-pentamethyl-2,3-dihydrobenzofuran-5-yl)sulfonyl)imino)imidazolidin-1-yl)pentanoate (21_{allyl})



21_{allyl}

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.82 (s, 1H) 7.75 (d, *J* = 7.5, 2H), 7.60 (d, *J* = 7.5, 2H), 7.38 (t, *J* = 7.0, 2H), 7.30 (t, *J* = 7.0, 2H), 5.86 (m, 1H), 5.31 (d, *J* = 17.2, 1H), 5.24 (d, *J* = 10.4, 1H), 4.60 (m, 2H), 4.37 (m, 3H) 4.20 (m, 2H), 3.53 (m, 2H), 2.95 (s, 2H), 2.58 (s, 3H), 2.52 (s, 3H), 2.11 (s, 3H), 1.84 (b, 1H), 1.66 (m, 3H), 1.46 (m, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 174.27, 172.17, 159.85, 156.35, 155.43, 155.41, 144.28, 144.17, 141.70, 139.35, 133.27, 131.85, 131.55, 128.13, 127.51, 125.57, 125.36, 120.40, 119.51, 118.21, 87.16, 77.81, 77.55, 77.30, 67.53, 66.50, 54.40, 54.02, 47.54, 43.48, 39.32, 30.08, 30.03, 28.98, 24.29, 24.23, 19.62, 18.34, 17.79, 12.86.

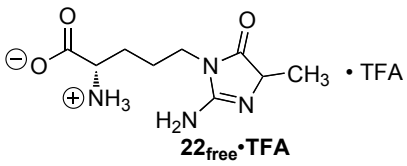
(2*S*)-2-((((9*H*-fluoren-9-yl)methoxy)carbonyl)amino)-5-((*E*)-4-methyl-5-oxo-2-(((2,2,4,6,7-pentamethyl-2,3-dihydrobenzofuran-5-yl)sulfonyl)imino)imidazolidin-1-yl)pentanoic acid (22)



22

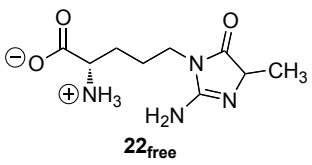
10% Pd/C (4.49 g, 4.22 mmol) was added to a flask containing fully protected MG-H3 (**21**, 3.35g, 4.22 mmol). After purging the system with N_2 for 5 minutes, degassed MeOH (100 mL) was then carefully added via syringe. A gentle stream of H_2 was then bubbled into the black suspension, and the reaction was stirred for 10 minutes, by which time starting material was fully consumed. After re-purging the system with N_2 for 5 minutes, the black solid was filtered over a thick pad of celite and washed with MeOH (1500 mL). The solvent was then removed under vacuum to give crude material as a gray solid. Purification was performed using Teledyne Isco with a normal phase 40 g Redi*Sep* column as the stationary phase. CH_2Cl_2 and MeOH were used as the mobile phase. Column conditions: 100% CH_2Cl_2 for 1 column volume followed by 0 → 20% MeOH over 15 column volumes and then 20% MeOH for 15 column volumes. Fmoc-(MG-H3)-Pbf **22** was isolated in 64% yield (1.89 g, 2.69 mmol) as an amorphous pale white solid possessing the following spectral characteristics: ^{1}H NMR (500 MHz, DMSO) δ 12.64 (b, 1H), 8.79 (s, 1H), 7.89 (d, *J* = 7.5, 2H), 7.72 (d, *J* = 7.5, 2H), 7.64 (d, *J* = 8.1, 1H), 7.41 (t, *J* = 7.4, 2H), 7.32 (t, *J* = 7.4, 2H), 4.31 – 4.16 (m, 4H), 3.89 (s, 1H), 3.38 (s, 2H), 2.96 (s, 2H), 2.51 (s, 3H), 2.46 (s, 3H), 2.02 (s, 3H), 1.73 – 1.46 (m, 4H), 1.40 (s, 6H), 1.33 (d, *J* = 7.0, 3H). ^{13}C NMR (126 MHz, DMSO) δ 174.28, 173.56, 173.53, 158.19, 156.09, 154.24, 143.80, 143.75, 140.69, 137.97, 132.22, 132.09, 127.59, 127.04, 125.26, 124.71, 120.06, 116.63, 86.65, 65.59, 53.95, 53.66, 53.63, 46.65, 42.25, 38.37, 28.22, 28.11, 28.06, 24.47, 24.40, 18.86, 17.62, 16.69, 12.17. IR *f* (cm^{-1}) = 3342, 3018, 2975, 1713, 1619, 1260, 1088, 745. HR-MS $(M+1)^+$ = 703.2791 (experimental); exact mass = 703.2802 (theoretical) for $C_{37}H_{43}N_4O_8S$. $[\alpha]^{23}_D$ = +5.84 (c = 7.2 $CHCl_3$).

(2S)-2-amino-5-(2-amino-4-methyl-5-oxo-4,5-dihydro-1H-imidazol-1-yl)pentanoic acid (22_{free}•TFA).



22_{free}•TFA

TFA (5 mL) was added to a flask containing Fmoc-(MG-H3)-Pbf (**22**, 123 mg, 175 μmol). The reaction was stirred at room temperature for 48 hours, whereupon the solvent was removed under vacuum to give a black oil. To this was added 2 M NH_3 in ^{i}PrOH (10 mL), and the reaction was stirred at room temperature for 24 hours. The solvent was removed under vacuum, and the residue was dissolved in H_2O (2 mL) and washed with CH_2Cl_2 (2 x 2 mL). Purification was preformed using preparatory HPLC with a SunFire Prep C18 OBD 10 mm 19x150 mm reverse-phase column as the stationary phase. H_2O and MeCN both buffered with 0.1% formic acid were used as the mobile phase. HPLC conditions: UV collection 214 nm, flow rate 20 mL/min, 0% MeCN for 5 minutes followed by 0% → 100% MeCN linear gradient over 2 minutes. The HPLC fractions were combined and lyophilized to give free MG-H3, an amorphous white solid, as a formate salt in 65% yield (26.1 mg, 114 μmol). Dissolution of this material in TFA (0.1% in H_2O) followed by lyophilization quantitatively provided the corresponding TFA salt (**22_{free}•TFA**), which was found to possess the following spectral characteristics: ^{1}H NMR (400MHz, D_2O) δ 4.46 (q, J = 7.2, 1H), 3.94 (t, J = 6.0, 1H), 3.74 (t, J = 7.2, 1H), 3.41 (t, J = 6.8, 1H), 2.03-1.90 (m, 2H), 1.89-1.68 (m, 2H), 1.48 (d, J = 7.2, 1H), 1.47 (d, J = 7.2, 2H). ^{13}C NMR (126 MHz, D_2O) δ 177.25, 176.38, 172.08, 171.97, 163.28, 163.00, 162.71, 162.43, 157.69, 155.86, 119.92, 117.60, 115.28, 112.95, 100.01, 55.66, 55.17, 54.54, 52.80, 52.64, 42.53, 41.48, 39.12, 39.07, 27.03, 26.87, 24.30, 23.49, 22.87, 22.55, 15.39. IR f (cm^{-1}) = 3097, 1179, 1673, 1550, 1432, 1321, 1201, 1137, 839, 800, 723. HR-MS $(M+1)^{+}$ = 229.1283 (experimental); exact mass = 229.1295 (theoretical) for $C_9H_{16}N_4O_3$.



22_{free}

The TFA salt (**22_{free}•TFA**) was then quantitatively converted into the free base (**22_{free}**) by titration with KOD. This material was found to possess the following spectral characteristics: ^{1}H NMR (400MHz, D_2O pH 10.07) 4.14 (m, 1H, ζ-H'), δ 4.08 (q, J = 7.2, 1H, ζ-H), 3.55 (m, 1H), 3.37 (m, 1H), 3.26 (m, 1H), 1.80-1.54 (m, 4H), 1.34 (m, 2H, η-H), 1.30 (d, J = 7.2, 2H, η–H').

GENERAL PROCEDURE FOR PEPTIDE SYNTHESIS.

Solid-Phase Peptide Synthesis (SPPS) was performed in a CEM Discover Liberty Microwave Peptide Synthesizer. The amount of resin, amino acids, and reagents used in the synthesis were calculated using manufacture suggested protocols based on 0.1 mmol scale synthesis. Upon completion of SPPS, the resin was collected through vacuum filtration and rinsed several times with CH_2Cl_2. After drying in open air, the resin was then added to a flask containing either cleavage cocktail mixture A or B and gently stirred for the time specified below. Subsequently, the resin was filtered through a cotton-plugged pipet, and the filtrate was directly collected into a 50 mL conical tube containing 35 mL of cold (-78°C) Et_2O, at which point a white precipitate immediately formed. The suspension was re-cooled to -78°C and then centrifuged at 4400 rpm for 5 minutes. After decanting the supernatant, the residual pellet was taken up in 50% MeCN/H_2O and purified using reverse-phase HPLC in 6-7 portions. The HPLC

fractions were combined and freeze-dried to give the corresponding peptides as white fluffy material.

Cleavage cocktail mixture A: 90:10:4:4:4 mixture of TFA:MsOH:Anisole:TIPS:H_2O
Cleavage cocktail mixture B: 96:4:4 mixture of TFA:TIPS:H_2O

Unless otherwise noted, preparatory HPLC was performed with a SunFire Prep C18 OBD 10 mm 19x150 mm reverse-phase column as the stationary phase. H_2O and MeCN both buffered with 0.1% formic acid were used as the mobile phase. HPLC conditions: UV collection 214 nm, flow rate 20 mL/min, 0% MeCN for 5 minutes followed by 0% → 20% MeCN linear gradient over 20 minutes. The HPLC fractions were combined and lyophilized to give the corresponding peptide as a formate salt. Unless otherwise noted, analytical HPLC was performed with a SunFire C18 5 mm 4.6x150 mm reverse-phase column as the stationary phase. H_2O and MeCN both buffered with 0.1% TFA were used as the mobile phase. Typical conditions: UV detection 214 nm, flow rate 1 mL/min, 0% MeCN for 5 minutes followed by 0% → 50% MeCN linear gradient over 50 minutes.

The molecular weight of the hydroimidazolone-containing peptides was determined by High Resolution Mass Spectrometry (HR-MS), which was performed at the W. M. Keck Foundation Biotechnology Resource Laboratory at Yale University.

LG-(MG-H1)-AG (23)

SPPS was performed using MG-H1 building block **12** starting with Fmoc-Gly-Wang Resin (100-200 mesh). Upon completion, the air-dried resin was treated with cleavage cocktail mixture A for 6 hours. The peptide was isolated in 32% yield (18.2 mg, >95% pure) as a white fluffy solid.
Prep HPLC Retention Time: 8.88 min
HR-MS: $(M+1)^+$ = 527.2935 (experimental); exact mass = 527.2936 (theoretical)

^{1}H NMR (500 MHz, D_2O) δ 4.40 – 4.36 (m, 3H; MG-H1 α-H, ζ-H, Ala α-H), 4.09 (t, *J* = 7.0, 1H; Leu α-H), 4.05 (s, 2H; Gly α-2H), 3.83 (d, *J* = 17.3, 1H; Gly α-2H), 3.77 (d, *J* = 17.3, 1H; Gly α-2H), 3.40 – 3.37 (m, 2H; MG-H1 δ-2H), 2.01 – 1.62 (m, 7H; Leu γ-H, β-2H, MG-H1 β-2H, γ-2H), 1.47 (d, *J* = 7.1, 3H; MG-H1 η-3H), 1.44 (d, *J* = 7.2, 3H; Ala β-2H), 0.99 (t, *J* = 6.3, 6H; Leu δ-6H).

LG-(MG-H2)-AG (24)

SPPS was performed using MG-H2 building block **18** starting with Fmoc-Gly-Wang Resin (100-200 mesh). Upon completion, the air-dried resin was treated with cleavage cocktail mixture B for 3 hours. The peptide was isolated in 33% yield (18.8 mg, >95% pure) as a white fluffy solid.
Prep HPLC Retention Time: 8.97 min
HR-MS: $(M+1)^+$ = 527.2923 (experimental); exact mass = 527.2936 (theoretical)

^{1}H NMR (500 MHz, D_2O) δ 4.46 – 4.31 (m, 3H; MG-H2 α-H, ζ-H, Ala α-H), 4.09 (t, *J* = 7.1, 1H; Leu α-H), 4.08 (d, *J* = 16.8, 1H; Gly α-2H), 4.03 (d, *J* = 16.8, 1H; Gly α-2H), 3.82 (d, *J* = 17.3, 1H; Gly α-2H), 3.77 (d, *J* = 17.3, 1H; Gly α-2H), 3.59 (m, 1H; MG-H2 δ-2H), 3.48 (m,

1H; MG-H2 δ-2H), 1.98 – 1.64 (m, 7H; Leu γ-H, β-2H, MG-H2 β-2H, γ-2H), 1.48 (d, *J* = 7.1, 3H; MG-H2 η-3H), 1.43 (d, *J* = 7.2, 3H; Ala β-2H), 0.99 (t, *J* = 6.5, 6H; Leu δ-6H).

LG-(MG-H3)-AG (25)

SPPS was performed using MG-H3 building block **22** starting with Fmoc-Gly-Wang Resin (100-200 mesh). Upon completion, the air-dried resin was treated with cleavage cocktail mixture A for 6 hours. The peptide was isolated in 47% yield (26.9 mg, >95% pure) as a white fluffy solid.
Prep HPLC Retention Time: 9.24 min
HR-MS: $(M+1)^+$ = 527.2934 (experimental); exact mass = 527.2936 (theoretical)

^{1}H NMR (500 MHz, D_2O) δ 4.48 (q, *J* = 7.1, 1H; MG-H3 α-H), 4.41 (q, *J* = 7.5, 1H; MG-H3 ζ-H), 4.39 (t, *J* = 7.5, 1H; Ala α-H), 4.09 (t, *J* = 7.2, 1H; Leu α-H), 4.04 (s, 2H; Gly α-2H), 3.82 (d, *J* = 17.3, 1H; Gly α-2H), 3.75(d, *J* = 17.3, 1H; Gly α-2H), 3.76 – 3.66 (m, 2H; MG-H3 δ-2H), 1.96 – 1.65 (m, 7H; Leu γ-H, β-2H, MG-H3 β-2H, γ-2H), 1.49 (d, *J* = 7.1, 3H; MG-H3 η-3H), 1.43 (d, *J* = 7.2, 3H; Ala β-2H), 0.99 (t, *J* = 6.3, 6H; Leu δ-6H).

LLV-R-YTKKV (26)
SPPS was performed starting with Fmoc-Val-Wang Resin (100-200 mesh). Upon completion, the air-dried resin was treated with cleavage cocktail mixture B for 90 minutes. The peptide was isolated in 46% yield (52.0 mg, >95% pure) as white fluffy solid.
Prep HPLC Retention Time: 12.65 min
Analytical HPLC Retention Time: 27.54 min
HR-MS: $(M+1)^+$ = 1119.7237 (experimental); exact mass = 1119.7248 (theoretical)

LLV-(MG-H1)-YTKKV (27)
SPPS was performed using MG-H1 building block **12** starting with Fmoc-Val-Wang Resin (100-200 mesh). Upon completion, the air-dried resin was treated with cleavage cocktail mixture A for 12 hours. Peptide was isolated in 59% yield (78.0 mg, >95% pure) as white fluffy solid.
Prep HPLC Retention Time: 14.15 min
Analytical HPLC Retention Time: 27.58 min
HR-MS: $(M+1)^+$ = 1173.7354 (experimental); exact mass = 1173.7354 (theoretical)

LLV-(MG-H2)-YTKKV (28)
SPPS was performed using MG-H2 building block **18** starting with Fmoc-Val-Wang Resin (100-200 mesh). Upon completion, the air-dried resin was treated with cleavage cocktail mixture B for 3 hours. The peptide was isolated in 37% yield (48.8 mg, >95% pure) as white fluffy solid.
Prep HPLC Retention Time: 13.42 min
Analytical HPLC Retention Time: 27.25 min
HR-MS: $(M+1)^+$ = 1173.7362 (experimental); exact mass = 1173.7354 (theoretical)

LLV-(MG-H3)-YTKKV (29)
SPPS was performed using MG-H3 building block **22** starting with Fmoc-Val-Wang Resin (100-200 mesh). Upon completion, the air-dried resin was treated with cleavage cocktail mixture A for 6 hours. The peptide was isolated in 55% yield (72.6 mg, >95% pure) as white fluffy solid.
Prep HPLC Retention Time: 13.48 min

Analytical HPLC Retention Time: 27.59 min
HR-MS: $(M+1)^+$ = 1173.7317 (experimental); exact mass = 1173.7354 (theoretical)

^{1}H NMR (500 MHz, DMSO) δ 8.62 (d, *J* = 8.0, 1H; Lys N-H), 8.14 (d, *J* = 7.5, 1H; Leu N-H), 8.01 (d, *J* = 7.5, 2H; Lys N-H, Thr N-H), 7.95 (d, *J* = 7.5, 1H; Tyr N-H), 7.83 (dd, 1H; Val N-H), 7.21 (t, *J* = 5.5, 1H; Val N-H), 6.98 (d, *J* = 8.0, 2H; Tyr aromatic-2H), 6.60 (d, *J* = 8.0, 2H; Tyr aromatic-2H), 4.51 (q, *J* = 7.5, 1H; Tyr α-H), 4.38 (q, *J* = 6.5, 1H; Leu α-H), 4.31 (q, *J* = 7.5, 1H; Lys α-H), 4.25 (q, *J* = 7.0, 1H; MG-H3 α-H), 4.20 (m, 1H; Thr α-H), 4.14 (q, *J* = 7.5, 1H; Val α-H), 4.08 (m, 1H; Lys α-H), 3.98-3.90 (m, 2H; MG-H3 α-H, Thr β-H), 3.72 (t, *J* = 5.5, 1H; Val α-H), 3.39 (m, 2H; MG-H3 δ–2H), 3.25 (t, *J* = 5.5, 1H; Leu α-H), 2.90-2.88 (m, 1H; Tyr β–H), 2.77-2.67 (m, 5H; 2 Lys δ-2H, Tyr β–H), 1.92 (m, 2H; 2 Val β–H), 1.73-1.21 (m, 20H; 2 Lys β–2H, 2 Lys γ-2H, 2 Lys δ–2H, 2 Leu β–2H, 2 Leu γ-H, MG-H3 β–2H, γ-2H), 1.18 (d, *J* = 7.0, 3H; MG-H3 η-3H), 1.00 (d, *J* = 6.0, 3H; Thr γ-3H), 0.87-0.75 (m, 24H; 2 Leu δ-6H, 2 Val γ-6H).

NLP-R-LV-R-PEV (30)
SPPS was performed starting with Fmoc-Val-Wang Resin (100-200 mesh). Upon completion, the air-dried resin was treated with cleavage cocktail mixture B for 90 minutes. The peptide was isolated in 33% yield (39.7 mg, >95% pure) as white fluffy solid.
Prep HPLC Retention Time: 18.74 min
Analytical HPLC Retention Time: 31.17 min
HR-MS: $(M+1)^+$ = 1192.7131 (experimental); exact mass = 1192.7160 (theoretical)

NLP-(MG-H1)-LV-(MG-H1)-PEV (31)
SPPS was performed using MG-H1 building block **12** starting with Fmoc-Val-Wang Resin (100-200 mesh). Upon completion, the air-dried resin was treated with cleavage cocktail mixture A for 12 hours. The peptide was isolated in 39% yield (50.7 mg, >95% pure) as white fluffy solid. Relevant analytical data are as follows:
Prep HPLC Retention Time: 21.29 min
Analytical HPLC Retention Time: 32.45 min
HR-MS: $(M+1)^+$ = 1300.7301 (experimental); exact mass = 1300.7372 (theoretical)

NLP-(MG-H2)-LV-(MG-H2)-PEV (32)
SPPS was performed using MG-H2 building block **18** starting with Fmoc-Val-Wang Resin (100-200 mesh). Upon completion, the air-dried resin was treated with cleavage cocktail mixture B for 3 hours. The peptide was isolated in 36% (46.3 mg, >95% pure) as white fluffy solid. *Note:* In addition to the standard analytical HPLC protocol described in the general information for peptide synthesis section, the analytical HPLC analysis of this peptide was also performed with a SunFire C18 5 mm 4.6x150 mm reverse-phase column as the stationary phase. H_2O and MeCN both buffered with 0.1% formic acid were used as the mobile phase. Typical conditions: UV detection 214 nm, flow rate 1 mL/min, 0% MeCN for 5 minutes followed by 0% → 50% MeCN linear gradient over 50 minutes. Relevant analytical data are as follows:
Prep HPLC Retention Time: 20.80 min
Analytical HPLC
Retention Time (mobile phase buffered with 0.1% TFA): 30.61 (minor), 30.92 (minor), 32.33 (major), 32.54 (major). These peaks presumably correspond to a mixture of

diastereomers at the MG-H2 ring systems and potentially their protonation states under HPLC conditions.

Retention Time (mobile phase buffered with 0.1% formic acid): 22.51 min
HR-MS: $(M+1)^+$ = 1300.7265 (experimental); exact mass = 1300.7372 (theoretical)

NLP-(MG-H3)-LV-(MG-H3)-PEV (33)
SPPS was performed using MG-H3 building block **22** starting with Fmoc-Val-Wang Resin (100-200 mesh). Upon completion, the air-dried resin was treated with cleavage cocktail mixture A for 6 hours. The peptide was isolated in 49% yield (64.1 mg, >95% pure) as white fluffy solid. Relevant analytical data are as follows:
Prep HPLC Retention Time: 20.58 min
Analytical HPLC Retention Time: 28.09 min
HR-MS: $(M+1)^+$ = 1300.7400 (experimental); exact mass = 1300.7372 (theoretical)

Bt-Ahx-LLV-R-YTKKV (Bt-26)
SPPS was performed starting with Rink resin. Upon completion, the air-dried resin was treated with cleavage cocktail mixture B for 90 minutes.
Prep HPLC Retention Time: 11.02 min
HR-MS: $(M+1)^+$ = 1457.8416 (experimental); exact mass = 1457.8792 (theoretical)

Bt-Ahx-LLV-(MG-H1)-YTKKV (Bt-27)
SPPS was performed using MG-H1 building block **12** starting with Rink resin. Upon completion, the air-dried resin was treated with cleavage cocktail mixture A for 12 hours.
Prep HPLC Retention Time: 18.00 min
HR-MS: $(M+1)^+$ = 1511.8816 (experimental); exact mass = 1511.8898 (theoretical)

Bt-Ahx-LLV-(MG-H2)-YTKKV (Bt-28)
SPPS was performed using MG-H2 building block **18** starting with Rink resin. Upon completion, the air-dried resin was treated with cleavage cocktail mixture B for 3 hours.
Prep HPLC Retention Time: 18.09 min
HR-MS: $(M+1)^+$ = 1511.8816 (experimental); exact mass = 1511.8898 (theoretical)

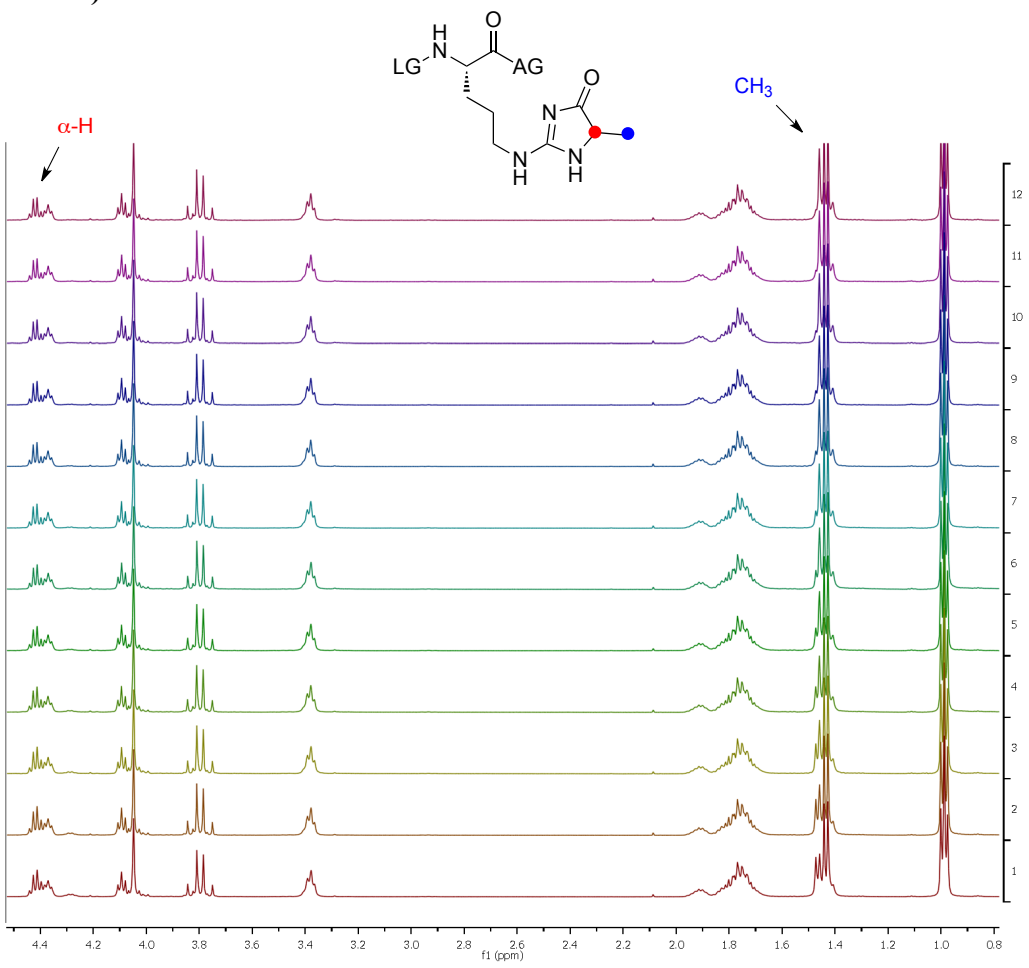
Bt-Ahx-LLV-(MG-H3)-YTKKV (Bt-29)
SPPS was performed using MG-H3 building block **22** starting with Rink resin. Upon completion, the air-dried resin was treated with cleavage cocktail mixture A for 6 hours.
Prep HPLC Retention Time: 18.00 min
HR-MS: $(M+1)^+$ = 1511.8324 (experimental); exact mass = 1511.8898 (theoretical)

Bt-Ahx-CRWRWKCCKK (Bt-CyLop-1)
SPPS was performed starting with Rink resin. Upon completion, the air-dried resin was treated with cleavage cocktail mixture B for 3 hours.
Prep HPLC Retention Time: 16.07 min
HR-MS: $(M+2)^{2+}$ = 1735.8107 (experimental); exact mass = 1735.8772 (theoretical)

PROTON-DEUTERIUM EXCHANGE STUDIES.

General Procedure: The indicated peptides (approximately 6.0 mg) were dissolved in D_2O (0.7 mL, 99.96% D), and the solution was added to a 5 mm NMR tube. ^1H NMR was immediately acquired, and subsequent acquisitions were executed every hour for 140 hours. Integrations of the disappearing α-H of the hydroimidazolone ring were compiled and plotted against time of spectrum acquisition using GraphPad Prism.

LG-(MG-H1)-AG



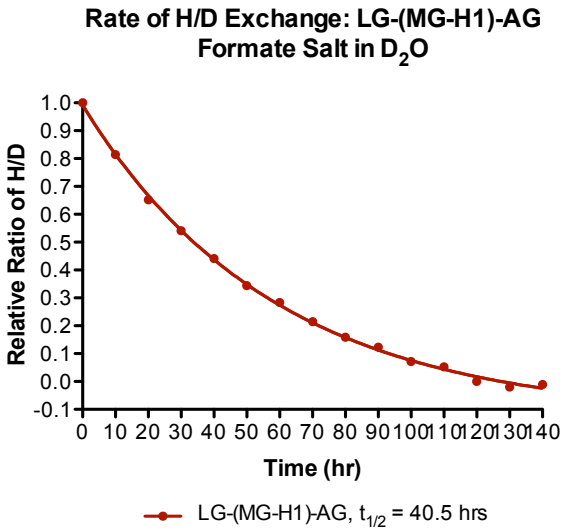
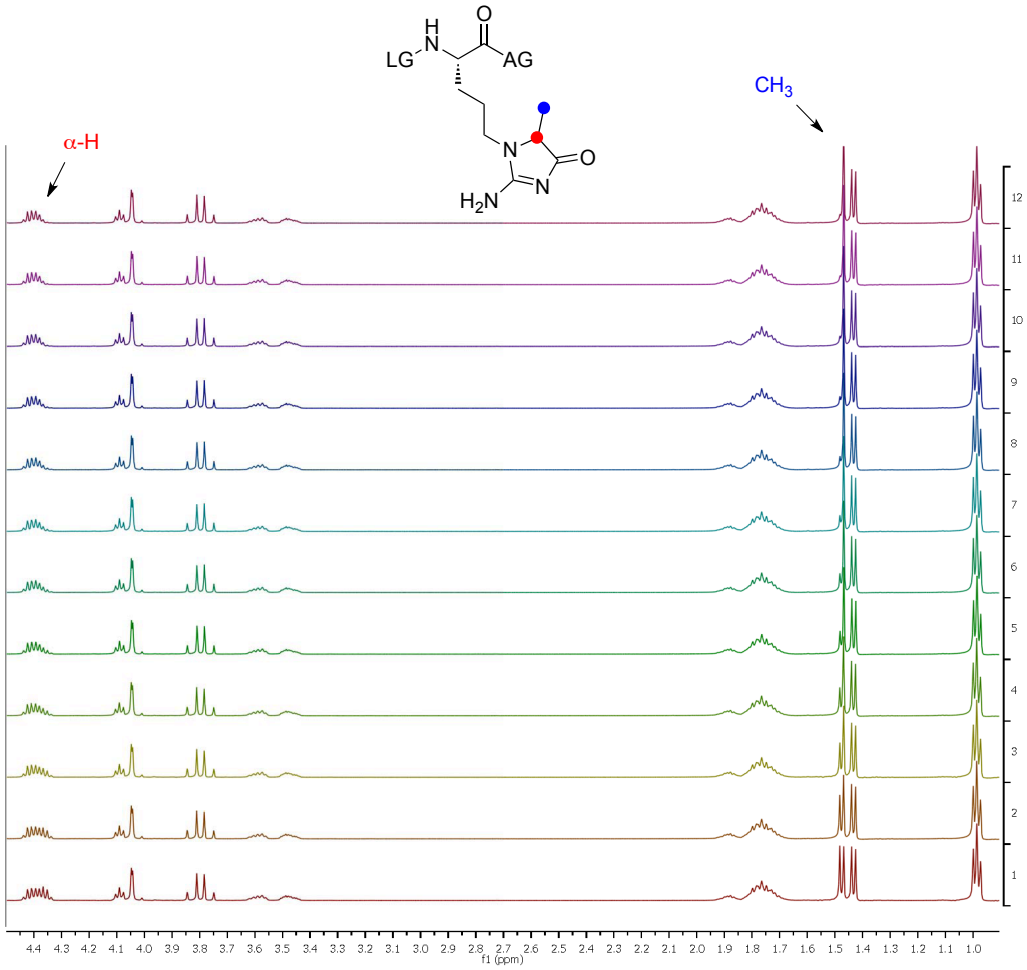


Figure S1. Rate of H/D Exchange of LG-(MG-H1)-AG in D_2O

LG-(MG-H2)-AG



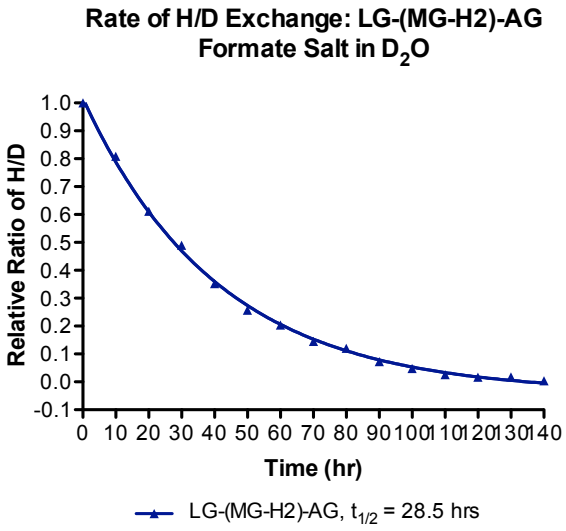
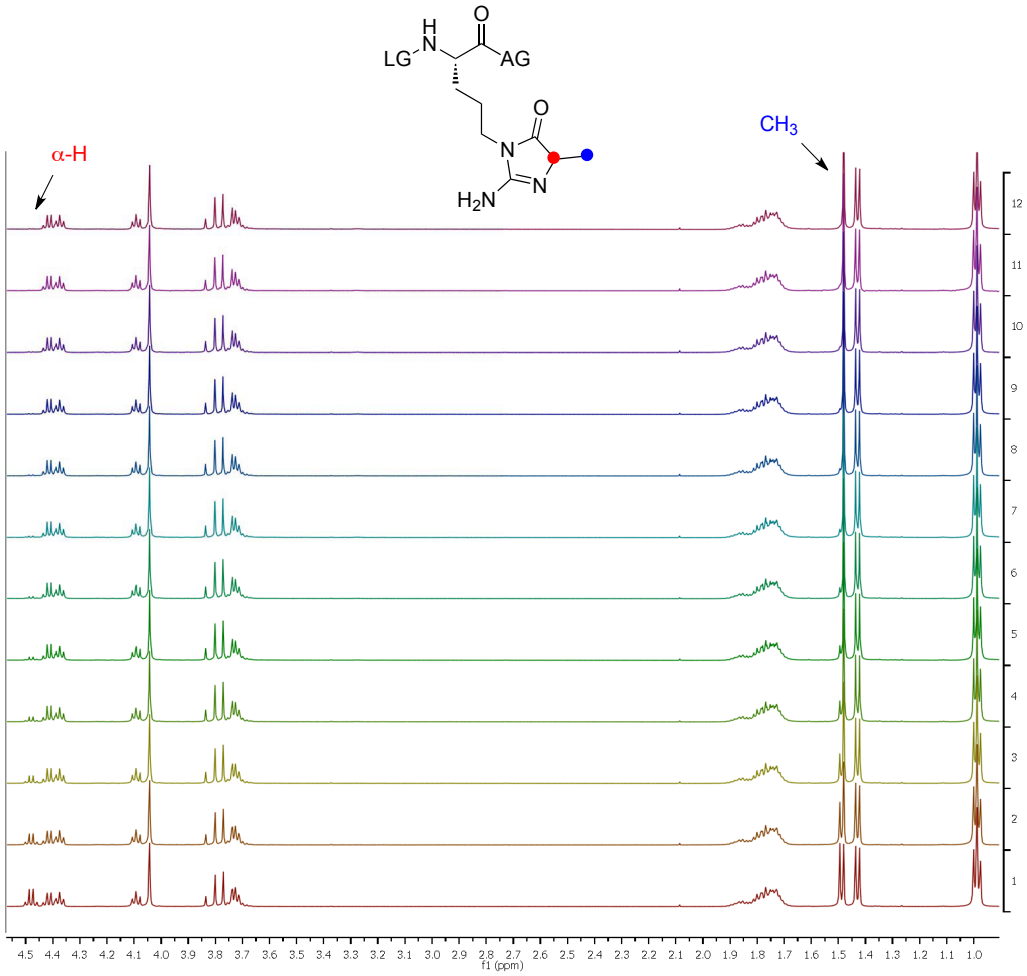


Figure S2. Rate of H/D Exchange of LG-(MG-H2)-AG in D_2O

LG-(MG-H3)-AG



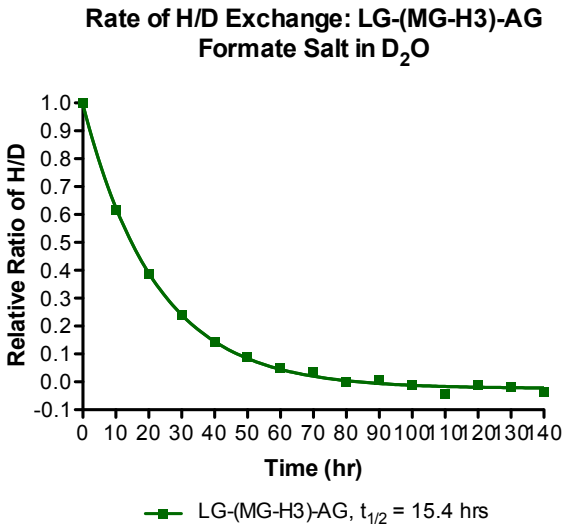


Figure S3. Rate of H/D Exchange of LG-(MG-H3)-AG in D_2O

COMPUTATIONAL STUDIES.

Calculations were done using the Gaussian 09 software package.[4] All geometry optimizations and frequency calculations were performed using DFT at the B3LYP/6-31+G(d) level of theory, while single-point energies were determined using B3LYP/6-311++G(2df,2p). All calculations implemented a polarizable continuum model for water solvation. Zero-point and free energy corrections obtained from frequency calculations were applied wherever appropriate. Values for pKa were determined according to a previously described method.[5]

Bond dissociation energy (BDE) is defined by the following reaction:

$$H\text{-}R \longrightarrow H\bullet + R\bullet$$

$$BDE = E(H\bullet) + E(R\bullet) - E(H\text{-}R)$$

Ionization energy (IE) is defined by the following reaction:

$$R \longrightarrow R^{\bullet+} + e^-$$

$$IE = E(R^{\bullet+}) - E(R)$$

ΔG_{ox} is defined by the following reaction:

$$R\text{-}H_2 \longrightarrow R + H_2$$

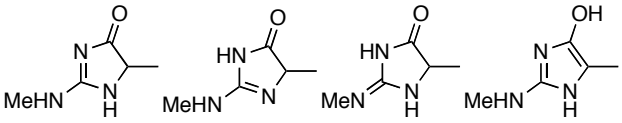
$$\Delta G_{ox} = E(R) + E(H_2) - E(R\text{-}H_2)$$

The relative energies of the MG-Hs' various tautomeric forms are shown in Tables S1-S3. These calculations were conducted in order to predict the lowest energy tautomers of each MG-H isomer, which were subsequently used for the BDE/IE determinations reported in the manuscript. Interestingly, in the case of MG-H3 there is only a small predicted energetic difference between tautomers **38a** and **38b** (Table S4). However, **38a** was calculated to possess a significantly lower BDE and IE compared to **38b**.

Similarly, the relative energies of the MG-Hs' various protonated forms were determined in order to predict the lowest energy protonated forms of each MG-H isomer (Table S5), which

were subsequently used for the pKa calculations reported in the manuscript. Note that **39a** and **42a** are resonance forms and therefore have the same energy.

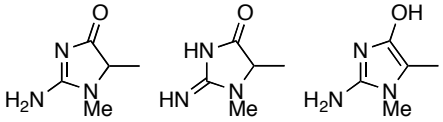
Table S1. Calculated Energies for MG-H1 tautomeric forms.



(36a) **(36b)** **(36c)** **(36d)**

Cmpd	ΔG (kcal/mol)	BDE (kcal/mol)	IE (kcal/mol)
36a	0.0	76.2	153.2
36b	6.15	n.d.	n.d.
36c	5.50	n.d.	n.d.
36d	17.94	n.d.	n.d.

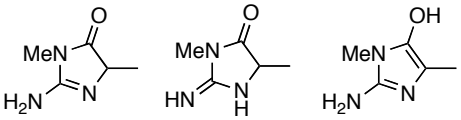
Table S2. Calculated Energies for MG-H2 tautomeric forms.



(37a) **(37b)** **(37c)**

Cmpd	ΔG (kcal/mol)	BDE (kcal/mol)	IE (kcal/mol)
37a	0.0	76.5	150.6
37b	4.55	n.d.	n.d.
37c	15.99	n.d.	n.d.

Table S3. Calculated Energies for MG-H3 tautomeric forms.



(38a) **(38b)** **(38c)**

Cmpd	ΔG (kcal/mol)	BDE (kcal/mol)	IE (kcal/mol)
38a	0.0	68.3	141.0
38b	-0.02	73.2	150.1
38c	15.96	n.d.	n.d.

Table S4. Calculated Energies for MG-H protonated forms.

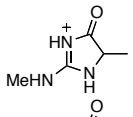
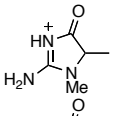
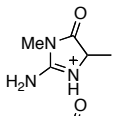
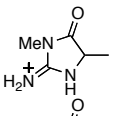
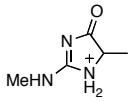
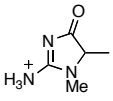
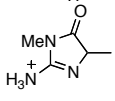
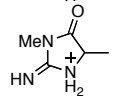
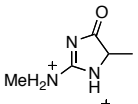
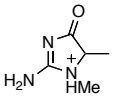
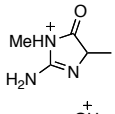
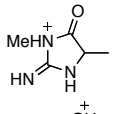
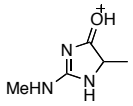
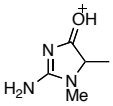
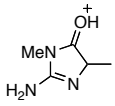
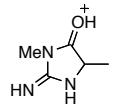
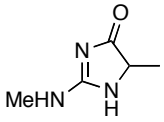
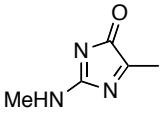
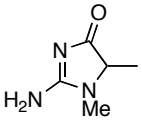
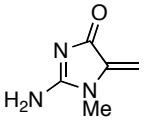
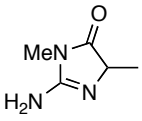
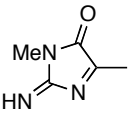
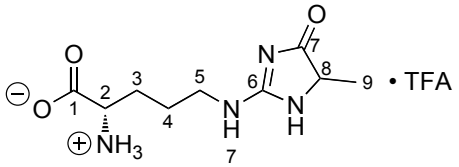
Cmpd	Structure	ΔG (kcal/mol)	Cmpd	Structure	ΔG (kcal/mol)	Cmpd	Structure	ΔG (kcal/mol)	Cmpd	Structure	ΔG (kcal/mol)
40a		0.0	**41a**		0.0	**39a**		0.0	**42a**		0.0
40b		25.0	**41b**		32.3	**39b**		30.8	**42b**		27.4
40c		30.0	**41c**		28.0	**39c**		43.3	**42c**		46.4
40d		12.3	**41d**		12.1	**39d**		27.5	**42d**		29.5

Table S5. Calculated Energies for hydroimidazolone and imidazolone isomers

Cmpd	Structure	ΔG (kcal/mol)	Cmpd	Structure	ΔG (kcal/mol)
36		0.0	**43**		0.0
37		-0.94	**44**		-3.55
38		2.39	**45**		0.60

STRUCTURAL ASSIGNMENTS AND COMPARISONS WITH REPORTED DATA.

I. COMPARISON OF 12_{free}•TFA WITH ISOLATED MG-H1 (REF. 6).



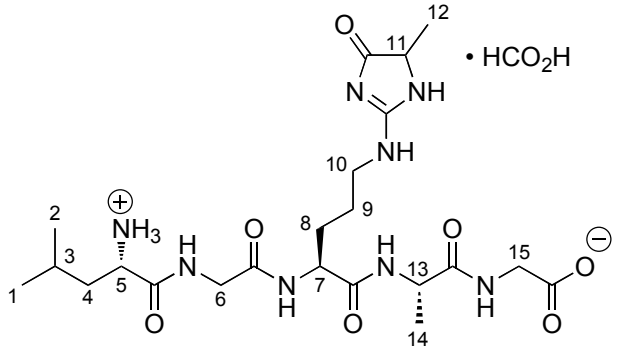
12_{free}•TFA

Comparison of ^{1}H NMR data			
Position (this work)	Position (ref. 6)	**12_{free}•TFA**, DMSO	MG-H1, HCl salt, DMSO (ref. 6)
2	(C-α)H	3.78 (m, 1H)	3.89 (m, 1H)
3	(C-β)H_2	1.63-1.85 (4H)	1.60-1.90 (4H)
4	(C-γ)H_2		

5	(C-δ)H_2	3.30 (m, 2H)	3.37 (q, 2H)
8	(C-5)H (A)	4.32 (q, 1H, $J_{H,CH3}$=6.8 Hz)	4.35 (dq, 1H, $J_{H,CH3}$=7.1 Hz, $J_{H,NH}$=1.7 Hz)
8	(C-4)H (B)	4.23 (q, 1H, $J_{H,CH3}$=6.8 Hz)	4.28 (q, 1H, $J_{H,CH3}$=7.1 Hz)
9	(C-5)CH_3 (A)	1.33 (d, 3H, $J_{CH3,H}$=6.8 Hz)	1.34 (d, 3H, $J_{CH3,H}$=7.1 Hz)
9	(C-4)CH_3 (B)	1.29 (d, 3H, $J_{CH3,H}$=6.8 Hz)	1.31 (d, 3H, $J_{CH3,H}$=7.1 Hz)

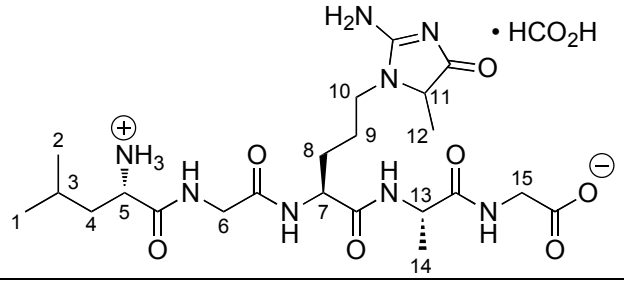
Comparison of ^{13}C NMR data			
Position (this work)	Position (ref. 6)	**12_{free}•TFA**, DMSO	MG-H1, HCl salt, DMSO (ref. 6)
1	COOH (A)	172.07	170.59
1	COOH (B)	172.07	170.59
2	C-α (A)	52.39	51.41
2	C-α (B)	52.32	51.41
3	C-β (A)	27.72	26.97
3	C-β (B)	27.52	26.84
4	C-γ (A)	24.34	23.90
4	C-γ (B)	25.24	24.69
5	C-δ (A)	41.35	41.21
5	C-δ (B)	42.22	41.99
6	C-2 (A)	157.61	155.94
6	C-2 (B)	Occluded by TFA	157.03
7	C-4 (A)	176.32	174.95
7	C-5 (B)	178.89	176.00
8	C-5 (A)	55.04	54.62
8	C-4 (B)	54.84	54.34
9	CH_3 (A)	16.41	15.89
9	CH_3 (B)	16.71	16.08

II. COMPARISON OF LG-(MG-H1)-AG WITH DATA IN REFERENCE 7



Comparison of ^{1}H NMR data			
Position (this work)	Position (ref. [7])	This work, formate salt, D_2O	Ref. [7], D_2O
7	MG-H1(α)-H	4.40-4.36 (m, 3H)	4.54-4.38 (m, 3H)
11	MG-H1(ζ)-H		
13	Ala(α)-H		
5	Leu(α)-H	4.09 (t, 1H, J=7.0 Hz)	4.15 (q, 1H, J=7.0 Hz)
15	Gly(α)-2H	4.05 (s, 2H)	4.11 (s, 2H)
6	Gly(α)-2H	3.83 (d, 1H, J=17.3 Hz), 3.77 (d, 1H, J= 17.3 Hz)	3.90 (d, 2H, J=5 Hz)
10	MG-H1(δ)-2H	3.40-3.37 (m, 2H)	3.46 (m, 2H)
3	Leu(γ)-H	2.01-1.62 (m, 7H)	1.97-1.73 (m, 7H)
4	Leu(β)-2H		
8	MG-H1(β)-2H		
9	MG-H1(γ)-2H		
12	MG-H1(η)-3H	1.47 (d, 3H, J=7.1 Hz)	1.55 (d, 3H, J=6.7 Hz)
14	Ala(β)-2H	1.44 (d, 3H, J=7.2 Hz)	1.49 (d, 3H, J=7.2 Hz)
1,2	Leu(δ)-6H	0.99 (t, 6H, J=6.3 Hz)	1.06 (d, 3H, J=5.6 Hz) 1.04 (d, 3H, J=5.6 Hz)

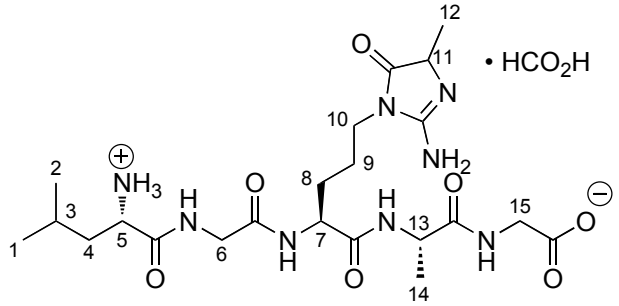
III. COMPARISON OF LG-(MG-H2)-AG WITH REFERENCE 7.



Comparison of ^{1}H NMR data			
Position (this work)	Position (ref. [7])	This work, formate salt, D_2O	Ref. [7], D_2O
7	MG-H2(α)-H	4.46-4.31 (m, 3H)	4.55-4.43 (m, 3H)
11	MG-H2(ζ)-H		
13	Ala(α)-H		
5	Leu(α)-H	4.09 (t, 1H, J=7.1 Hz)	4.15 (q, 1H, J=7.1 Hz)
15	Gly(α)-2H	4.08 (d, 1H, J=16.8 Hz), 4.03 (d, 1H, J=16.8 Hz)	4.11 (s, 2H)
6	Gly(α)-2H	3.82 (d, 1H, J=17.3 Hz), 3.77 (d, 1H, J= 17.3 Hz)	4.00 (d, 2H, J=3.5 Hz)
10	MG-H2(δ)-2H	3.59 (m, 1H), 3.48 (m, 1H)	3.69 (m, 1H), 3.57 (m, 1H)

3	Leu(γ)-H	1.98-1.64 (m, 7H)	1.97-1.72 (m, 7H)
4	Leu(β)-2H		
8	MG-H2(β)-2H		
9	MG-H2(γ)-2H		
12	MG-H2(η)-3H	1.48 (d, 3H, J=7.1 Hz)	1.58 (d, 3H, J=7.1 Hz)
14	Ala(β)-2H	1.43 (d, 3H, J=7.2 Hz)	1.49 (d, 3H, J=7.2 Hz)
1,2	Leu(δ)-6H	0.99 (t, 6H, J=6.5 Hz)	1.06 (d, 3H, J=5.7 Hz), 1.04 (d, 3H, J=5.7 Hz)

IV. COMPARISON OF LG-(MG-H3)-AG WITH REF 7



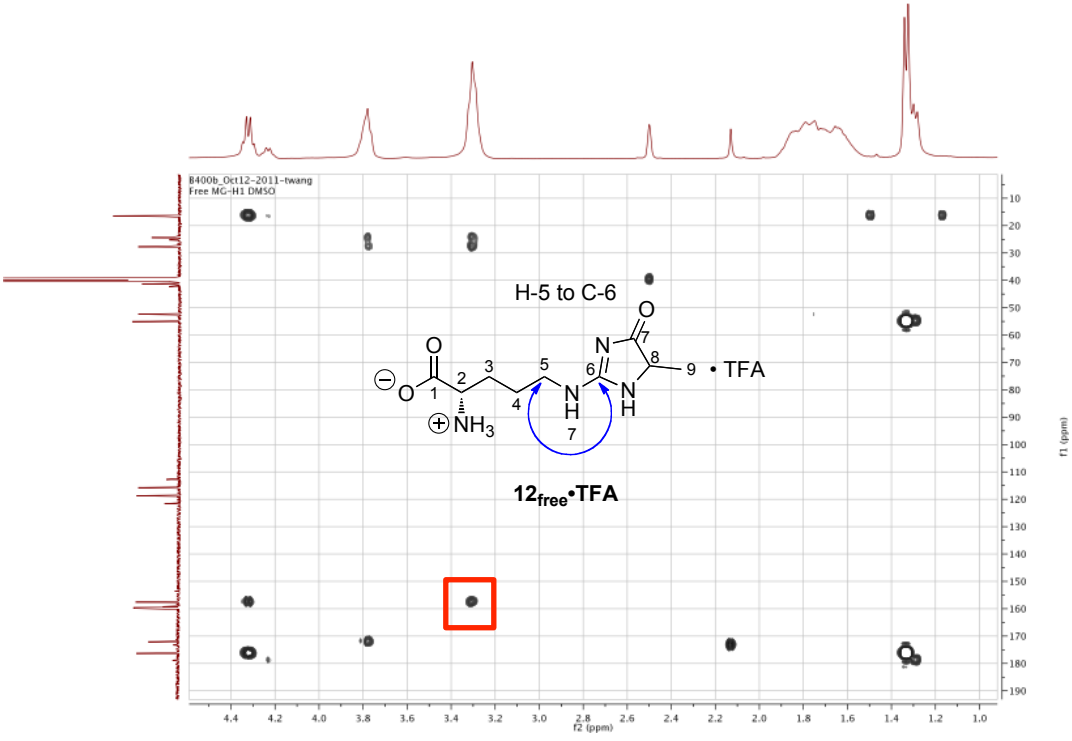
Comparison of ^{1}H NMR data			
Position (this work)	Position (ref. [7])	This work, formate salt, D_2O	Ref. [7], D_2O
7	MG-H3(α)-H	4.48 (q, 1H, J=7.1 Hz)	4.55-4.39 (m, 3H)
11	MG-H3(ζ)-H	4.41 (q, 1H, J=7.5 Hz)	
13	Ala(α)-H	4.39 (t, 1H, J=7.5 Hz)	
5	Leu(α)-H	4.09 (t, 1H, J=7.2 Hz)	4.14 (q, 1H, J=7.1 Hz)
15	Gly(α)-2H	4.04 (s, 2H)	4.09 (s, 2H)
6	Gly(α)-2H	3.82 (d, 1H *J* = 17.3 Hz), 3.75(d, 1H, *J* = 17.3 Hz)	3.83 (d, 2H, J=2 Hz)
10	MG-H3(δ)-2H	3.76-3.66 (m, 2H)	3.78 (m, 2H)
3	Leu(γ)-H	1.96-1.65 (m, 7H)	1.91-1.72 (m, 7H)
4	Leu(β)-2H		
8	MG-H3(β)-2H		
9	MG-H3(γ)-2H		
12	MG-H3(η)-3H	1.49 (d, 3H, J=7.1 Hz)	1.53 (d, 3H, J=6.8 Hz)
14	Ala(β)-2H	1.43 (d, 3H, J=7.2 Hz)	1.47 (d, 3H, J=7.2 Hz)
1,2	Leu(δ)-6H	0.99 (t, 6H, J=6.3 Hz)	1.04 (d, 3H, J=5.4 Hz), 1.03 (d, 3H, J=5.4 Hz)

V. ADDITIONAL SPECTRAL COMPARISONS

^{1}H and ^{13}C NMR spectra of **12$_{free}$•TFA**, **18$_{free}$•TFA**, and **22$_{free}$•TFA** in MeOD were also found to be consistent with previously reported values.[8]

VI. INDEPENDENT STRUCTURAL ASSIGNMENTS OF MG-H REGIOISOMERS

Independent verification of the regioisomeric assignments of the MG-Hs was done by HMBC experiments conducted on **12$_{free}$•TFA**, **18$_{free}$•TFA**, and **22$_{free}$•TFA**. Out of the three possible isomers, **18$_{free}$•TFA** is the only one expected to have coupling between sidechain carbon C-5 and the ring alpha proton H-8 (Figure S5), while **22$_{free}$•TFA** should be the only isomer to display coupling between H-5 and the ring carbonyl carbon C-7 (Figure S6). All three isomers should show coupling between H-5 and guanidine-like carbon C-6, which is the only sidechain-to-ring coupling seen in **12$_{free}$•TFA** (Figure S4).



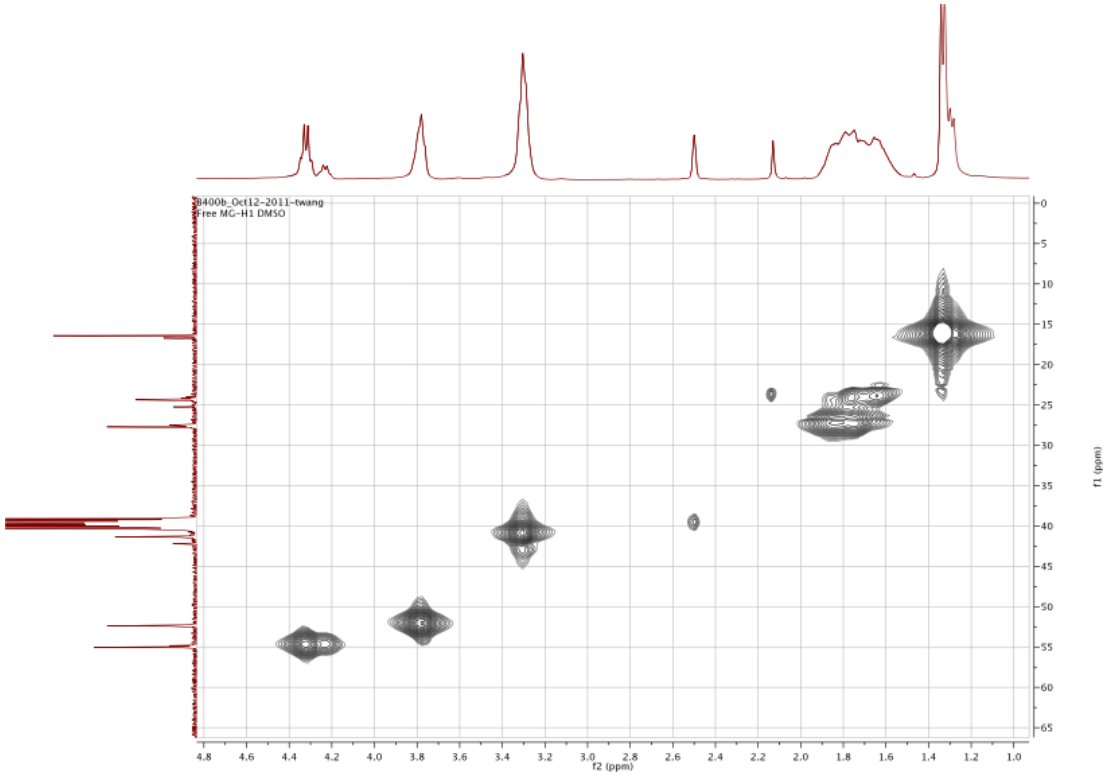
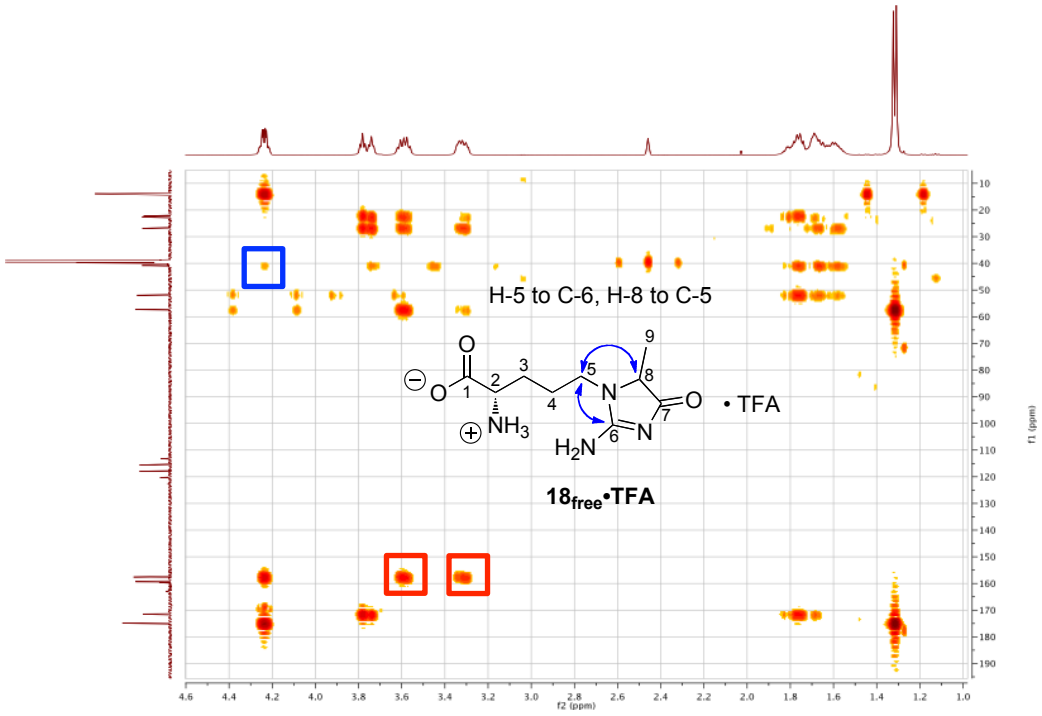


Figure S4. 2D NMR analysis of **12**$_{free}$•**TFA** in DMSO-d6. Top: HMBC spectrum, showing coupling between H-5 and C-6 (red box). Bottom: HSQC spectrum.



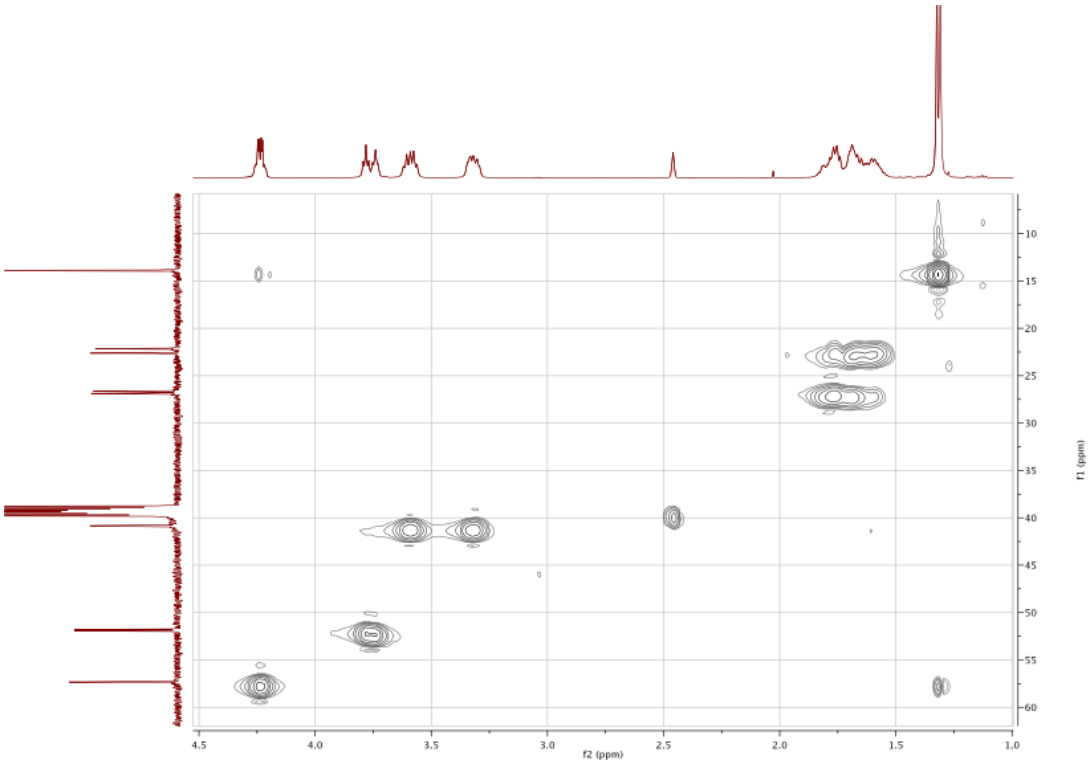
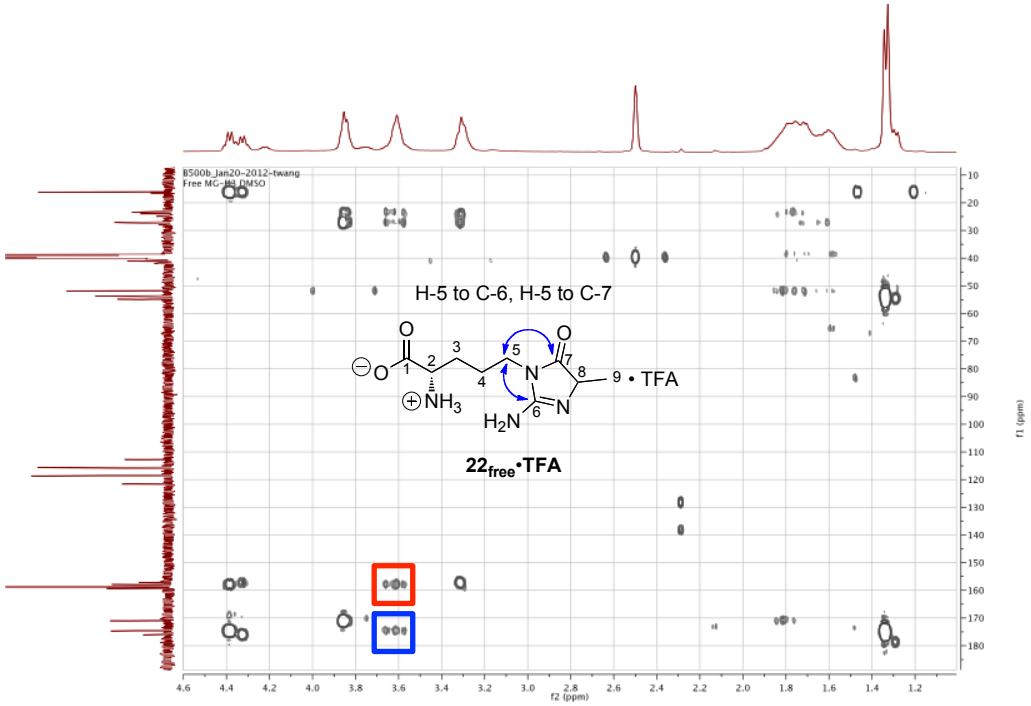


Figure S5. 2D NMR analysis of **18**$_{free}$**•TFA** in DMSO-d6. Top: HMBC spectrum showing coupling between H-5 and C-6 (red box), and H-8 and C-5 (blue box). Bottom: HSQC spectrum.



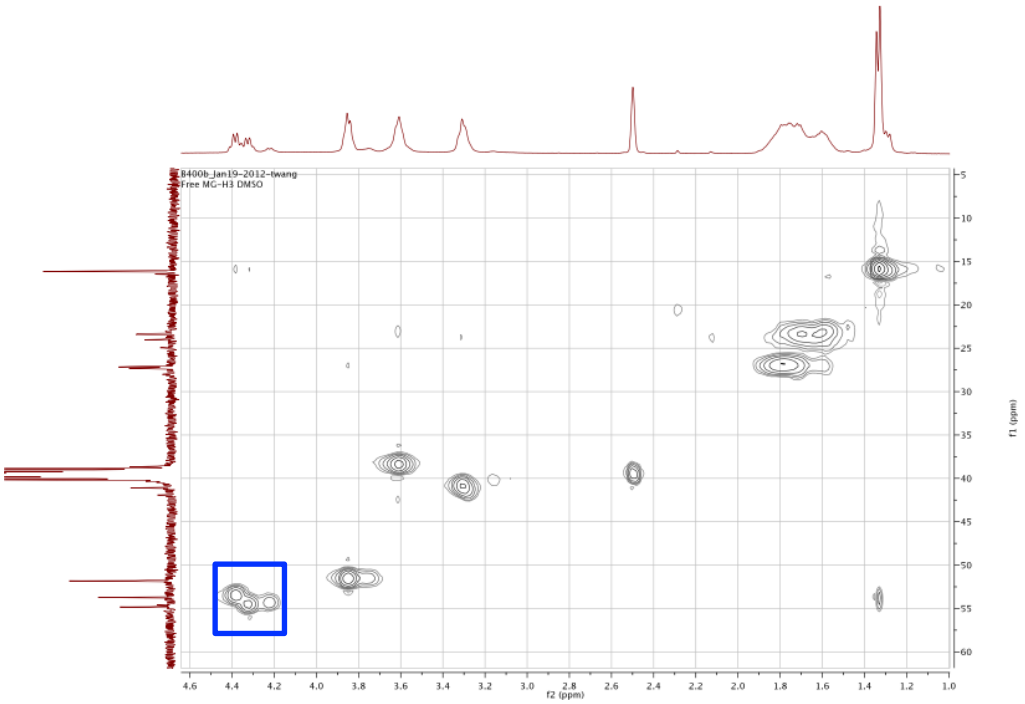
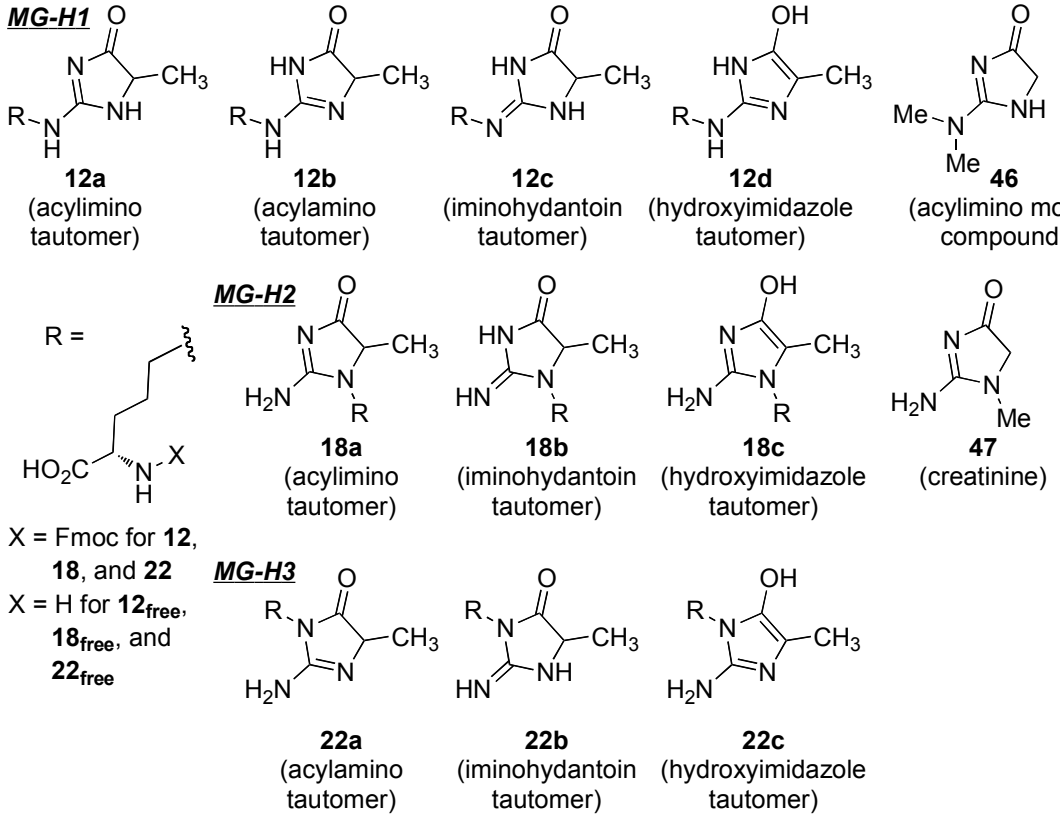


Figure S6. 2D NMR analysis of **22**$_{free}$**•TFA** in DMSO-d6. Top: HMBC spectrum showing coupling between H-5 and C-6 (red box), and H-5 and C-7 (blue box). Bottom: HSQC spectrum showing coupling at the ring methine position between H-8 and C-8 (blue box). For clarity, one tautomer is shown.

VII. ASSIGNMENT OF TAUTMERIC PREFERENCES

Scheme S4.



The MG-H ring heterocycles can exist in various tautomeric forms (Scheme S4). Tautomeric forms for each of these species was rigorously assigned on the basis of detailed spectroscopic analysis, and/or comparison with previously reported data as follows:

1. **MG-H1 series**. Hydroimidazolones **12** and **12**$_{\mathbf{free}}$. In theory, this compound can exist as acylimino (**12a**), acylamino (**12b**), iminohydantoin (**12c**), or hydroxyimidazole (**12d**) tautomers, as shown. Assignment as tautomer **12a** is based on direct comparison to 2-dimethylamino-2-imidazolin-4-one (**46**), a structural homologue of **12** whose tautomeric assignment has been unambiguously established.[9] This comparison is in full agreement with the DFT calculations shown in Table S2.
2. **MG-H2 series**.
   a. *Bis*-Boc-protected hydroimidazolone **18**. This compound is assigned as the only reasonable tautomer, given its substitution pattern.
   b. Hydroimidazolone **18**$_{\mathbf{free}}$. In theory, this compound can exist as acylimino (**18a**), iminohydantoin (**18b**), or hydroxyimidazole (**18c**) tautomers, as shown. Assignment as acylimino tautomer **18a** is based on direct comparison with creatinine (**47**), a close structural homologue of **18**$_{\mathbf{free}}$, whose tautomeric assignment has been unambiguously established.[9] This comparison is in full agreement with the DFT calculations shown in Table S2.
3. **MG-H3 series**.

a. Pbf-protected hydroimidazolone **22**. In theory, this compound can exist as acylimino (**22a**), iminohydantoin (**22b**), or hydroxyimidazole (**22c**) tautomers, as shown. Assignment as iminohydantoin tautomer **22b** is based on rigorous analysis of ^{1}H-NMR correlation spectra, depicted in Figure S7. The indicated COSY crosspeak is diagnostic for the iminohydantoin tautomer **18b**.

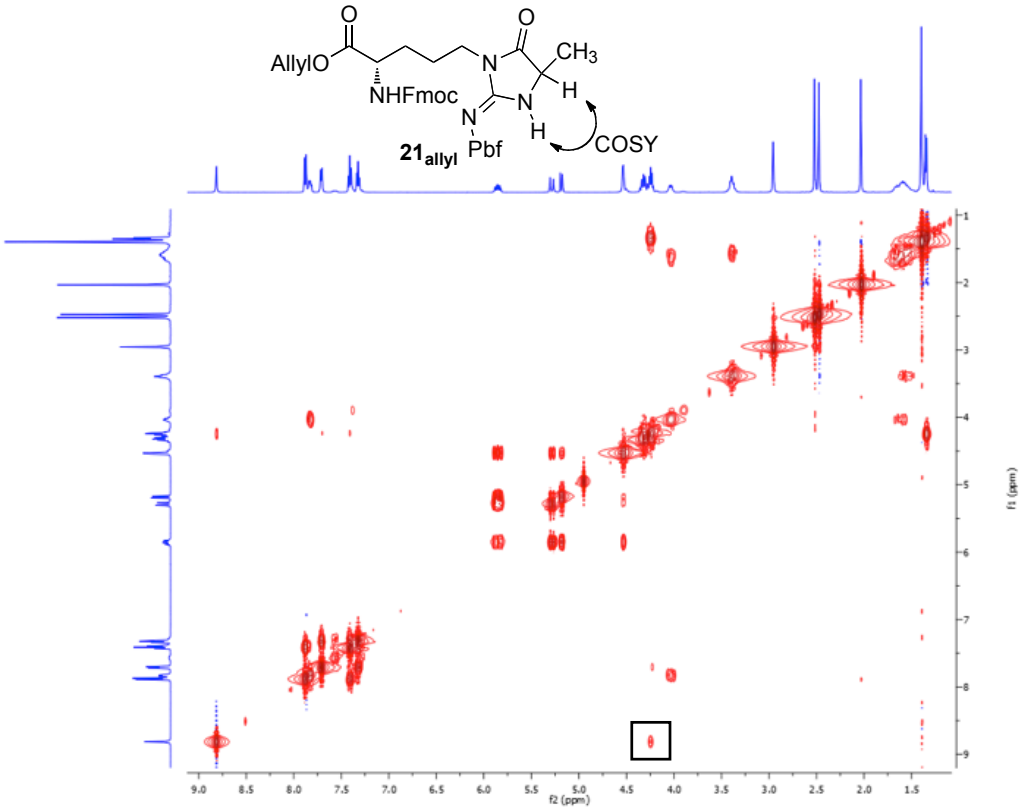


Figure S7. COSY NMR spectrum of **21**$_{\mathbf{allyl}}$, showing coupling indicative of the acylamino type I tautomer (box)

b. Hydroimidazolone **22**$_{\mathbf{free}}$. This compound can exist as acylamino (**22a**), iminohydantoin (**22b**), or hydroxyimidazole (**22c**) tautomers. Heteronuclear single-quantum correlation (HSQC) NMR experiments (see Figure S6, bottom) provide strong evidence for a methine C–H within the ring, readily ruling out tautomer **22c**. While computational studies (Figure S4) suggest that, based on its low BDE and IE values, tautomer **22a** is more likely consistent with results of redox assays (Figure 2), we cannot rule out the existence of both acylamino and iminohydantoin tautomers at this stage.

GENERAL INFORMATION FOR ANTIOXIDANT ASSAYS.

Unless otherwise noted, all micro-plate based assays were read on a BioTek Synergy 3 Microplate reader and data was fitted and graphed using GraphPad Prism version 5.00 for Mac OS X (GraphPad Software, San Diego California USA, www.graphpad.com). Liquid chromatography/mass spectroscopy (LC/MS) was performed on a Waters Acuity UPLC

equipped with Xevo QTof MS. Peptide solutions were diluted with water and separated on a BEH C18 column using a flow rate of 0.3mL/min. The mobile phase were H_2O buffered with 0.1% formic acid and CH_3CN buffered with 0.1% formic acid. For separation, the following method was used: 5% → 85% CH_3CN gradient over 5.25 minutes, then 95% CH_3CN for 2.25 minutes.

MTT ANTIOXIDANT ASSAY

The MTT antioxidant assay procedure was modified from a previously published method.[10] Test compounds were prepared as 4 mM stocks in DMSO. 200 µL of a 2.4 mM solution of 3-(4,5-dimethylthiazole-2-yl)-2,5-diphenyltetrazolium bromide (Sigma) in water was added to 10 µL of test compound solution and 190 µL DMSO in a glass vial. This mixture was vortexed, then allowed to incubate at room temperature for 24 h before a 200 µL aliquot was removed into a 96-well plate. 570 nm absorbance was read by plate reader. Each sample was assayed in triplicate, and is reported in the manuscript as the average of three trials ± standard deviation.

HR-MS/MS ANALYSIS OF MTT ASSAY PRODUCTS

MS/MS and high-resolution mass spectrometry analyses of the hydroimidazolone-containing peptides were performed at the W. M. Keck Foundation Biotechnology Resource Laboratory at Yale University. Peptide stocks (4 mM) were submitted as 1:100 dilutions in H_2O. Antioxidant assay mixtures were allowed to incubate as previously described and submitted as 1:5 dilutions in H_2O immediately following assay completion.

LLV-(MG-H3)-YTKKV (29)

Species	Predicted Mass	Experimental Mass
LLV-(MG-H3)-YTKKV	1173.7354	1173.7409
LV-(MG-H3)-YTKKV	1060.6519	1060.6445
V-(MG-H3)-YTKKV	947.5678	947.5534
(MG-H3)-YTKKV	848.4994	848.5047
YTKKV	638.3877	638.3906

LLV-(MG-I3)-YTKKV (34)

Species	Predicted Mass	Experimental Mass
LLV-(MG-I3)-YTKKV	1171.7203	1171.7256
LV-(MG-I3)-YTKKV	1058.6362	1058.6408
V-(MG-I3)-YTKKV	945.5522	945.5540
(MG-I3)-YTKKV	846.4838	846.4862
YTKKV	638.3877	638.3901

NLP-(MG-H3)-LV-(MG-H3)-PEV (33)

Species	Predicted Mass	Experimental Mass

NLP-(MG-H3)-LV-(MG-H3)-PEV	1300.7377	1300.7412
NLP-(MG-H3)-LV-(MG-H3)-PE	1073.6108	1073.6137
NLP-(MG-H3)-LV	766.4463	766.4451
NLP-(MG-H3)-L	653.3623	653.3641
NLP-(MG-H3)	554.2938	554.2949

NLP-(MG-I3)-LV-(MG-H3)-PEV

Species	Predicted Mass	Experimental Mass
NLP-(MG-H3)-LV-(MG-I3)-PEV	1298.7221	Not observed
NLP-(MG-H3)-LV-(MG-I3)-P	1071.5951	1071.5966
NLP-(MG-H3)-LV-(MG-I3)	974.5423	974.5442
NLP-(MG-H3)-LV	766.4463	766.4475
NLP-(MG-H3)-L	653.3623	653.3639
NLP-(MG-H3)	554.2938	554.2950

NLP-(MG-I3)-LV-(MG-I3)-PEV

Species	Predicted Mass	Experimental Mass
NLP-(MG-I3)-LV-(MG-I3)-PEV	1296.7064	Not observed
NLP-(MG-I3)-LV-(MG-I3)-P	1069.5795	1069.5859
NLP-(MG-I3)-LV-(MG-I3)	972.5267	972.5309
NLP-(MG-I3)-LV	764.4307	764.4791

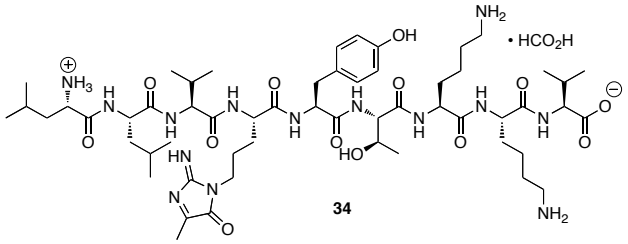
DPPH RADICAL SCAVENGING ASSAY

The DPPH radical scavenging assay was modified from a previously published method.[11] Test compounds were dissolved in water to a concentration of 4 mM, then 31.25 μL of stock solutions were further diluted with an equal amount of water along the first column of a 96-well plate. Serial dilutions (1:5) were then performed by aspirating 12.5 μL from each well in this first column using a multichannel pipettor, and dispensing this into a 50 μL volume of water in each well in the second column. Serial repetition of this procedure yielded a final volume of 50 μL in each well. The last column of wells contained no test compound. Then, 50 μL of 40 mM pH 7.0 phosphate/citrate buffer was added to each well on the plate to yield a final volume of 100 μL per well. A freshly prepared solution of DPPH in ethanol (0.1 mg/mL, 100 μL) was then added to each well with a multichannel pipette. The plate was allowed to incubate in the dark at room temperature for 1 hour before 515 nm absorbance was read by plate reader. IC_{50} values were calculated using nonlinear least-squares regression. Each sample was assayed in triplicate, and is reported in the manuscript as the average of three trials ± standard deviation.

To assay the dependence of MG-H3-mediated DPPH scavenging on pH, 15 μL of a 4 mM solution of LLV-(MG-H3)-YTKKV or ascorbic acid in water was added to 35 μL water and 50 μL of 40 mM phosphate/citrate buffer at pH 4.0, 5.0, 6.0, and 7.0 in a 96-well plate. A set of blanks were also included, consisting of 50 μL of the buffer and 50 μL of water. 100 μL of a freshly prepared 0.1 mg/mL DPPH solution in ethanol was added to each well with a multichannel pipette. The plate was then read at 515 nm absorbance every minute for 1 h by

plate reader. Each sample was assayed in triplicate, and is reflected in the manuscript as the average of three trials ± standard deviation.

CHARACTERIZATION OF MG-H3 OXIDATION PRODUCT



LLV-(MG-H3)-YTKKV was oxidized to LLV-(MG-I3)-YTKKV using DPPH conditions as described above, and the product was isolated by HPLC. The preparatory HPLC was performed with a SunFire Prep C18 OBD 10 mm 19x150 mm reverse-phase column as the stationary phase. H_2O and MeCN both buffered with 0.1% formic acid were used as the mobile phase. HPLC conditions: UV collection 214 nm, flow rate 20 mL/min, 0% MeCN for 5 minutes followed by 0% → 20% MeCN linear gradient over 20 minutes. The HPLC fractions were combined and lyophilized to give the corresponding peptide as a formate salt. Analytical HPLC was performed with a SunFire C18 5 mm 4.6x150 mm reverse-phase column as the stationary phase. H_2O and MeCN both buffered with 0.1% formic acid were used as the mobile phase. Typical conditions: UV detection 214 nm, flow rate 1 mL/min, 0% MeCN for 5 minutes followed by 0% → 50% MeCN linear gradient over 50 minutes. Relevant analytical data are as follows:

Prep HPLC Retention Time: 22.95 min
Analytical HPLC Retention Time: 23.60 min
HR-MS: $(M+1)^+$ = 1171.7231 (experimental); exact mass = 1171.71976 (theoretical)
^{1}H NMR (500 MHz, DMSO) δ 8.60 (d, *J* = 8.0, 1H; Lys N-H), 7.91 (m, 3H; Lys N-H, Thr N-H, MG-H3 N-H), 7.85 (s, 1H; Tyr N-H), 7.69 (d, *J* = 9.0, 1H; Val N-H), 7.55 (d, *J* = 8.5, 1H; Leu N-H), 7.17 (d, *J* = 8.0, 1H; Val N-H), 7.00 (d, *J* = 8.0, 2H; Tyr aromatic-2H), 6.61 (d, *J* = 8.0, 2H; Tyr aromatic-2H), 4.55 (m, 1H; Tyr α-H), 4.33 (m, 3H; Leu α-H, Lys α-H, Val α-H), 4.19 (q, *J* = 8.5, 1H; Thr α-H), 4.12 (t, *J* = 8.0, 1H; MG-H3 α-H), 4.06 (m, 1H; Lys α-H), 3.91 (t, *J* = 5.5, 1H; Thr β–H), 3.69 (t, *J* = 5.5, 1H; Val α-H), 2.91 (d, *J* = 10.5, 1H; Tyr β–H), 2.70 (m, 5H; 2 Lys δ-2H, Tyr β–H), 2.22 (m, 1H; Val β–2H), 1.92 (m, 1H; Val β–2H), 1.81-1.15 (m, 25H; 2 Lys β–2H, 2 Lys γ-2H, 2 Lys δ–2H, 2 Leu β–2H, 2 Leu γ-H, MG-H3 β–2H, γ-2H, η-3H), 0.99 (d, *J* = 6.0, 3H; Thr γ-3H), 0.92-0.80 (m, 24H; 2 Leu δ-6H, 2 Val γ-6H).

Overlay of the oxidation product shows that, in MG-I3, the α proton of the ring disappears, while the ring methyl protons shift downfield (Figure S8). This is consistent with structure **34**, where the MG-H3 ring is oxidized upon loss of the hydrogen at the α position; the resultant C-N double bond would then be expected to shift the methyl proton resonances slightly downfield.

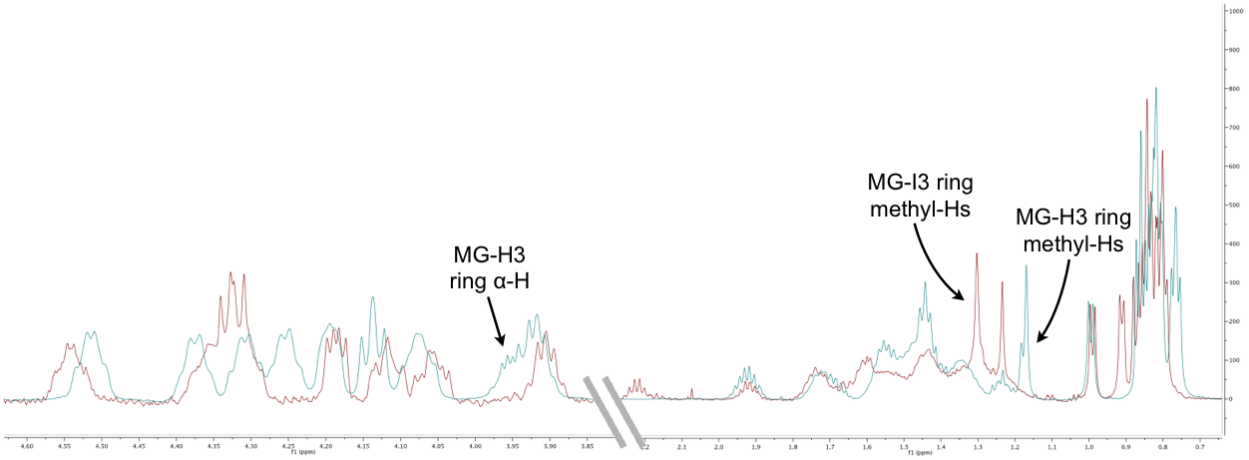


Figure S8. Overlay of oxidized peptide LLV-(MG-I3)-YTKKV (red) with starting material (blue)

HYDROLYSIS OF MG-H3 OXIDATION PRODUCT (MG-I3).

The isolated MG-I3 peptide was then dissolved in DPBS (Gibco) at 8.5 µM and incubated at 37ºC. Small aliquots were taken at various times and analyzed by LCMS, which indicated a time-dependent decrease in the parent peak and the simultaneous appearance of a new peak whose mass corresponded to that of the arginine-containing peptide (Figure S9). Coinjection of the reaction mixture at 23 hours with purified LLV-R-YTKKV showed a volume-dependent increase of the peak of the hydrolysis product (Figure S10).

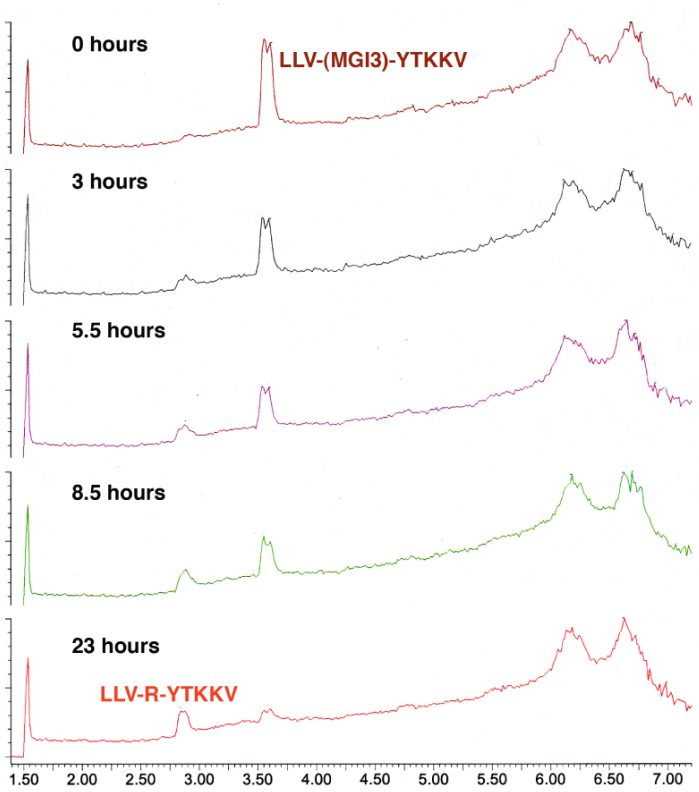


Figure S9. Incubation of LLV-(MG-I3)-YTKKV in DPBS at 37ºC results in the time-dependent emergence of a new peak accompanied by disappearance of starting material

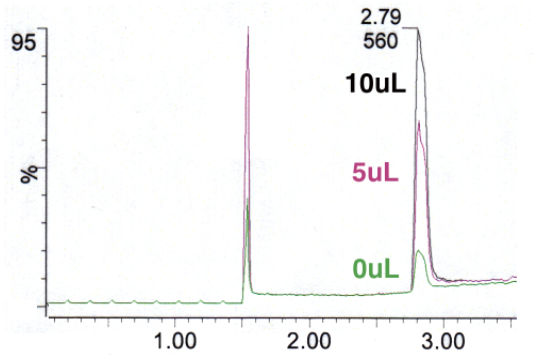


Figure S10. Co-injection of the hydrolysis product with 0, 5, or 10 µL of 0.4 mM purified LLV-R-YTKKV.

PYRUVATE DETECTION.

LLV-(MG-I3)-YTKKV (8.5 µM) was incubated in DPBS at 37ºC. At various times, small aliquots (10 µL) were taken of the mixture and frozen at -80ºC. These were then analyzed using a previously-reported method for enzymatic detection.[12] Briefly, 180 µL of a freshly-prepared cocktail consisting of 100M potassium phosphate buffer with 1.0 mM EDTA, pH 6.7, 1.0 mM $MgCl_2$, 10 µM FAD, 0.2 mM thiamine pyrophosphate (Sigma), 0.2 U/mL pyruvate oxidase (Sigma), 0.5 U/mL HRP (Sigma), and 50 µM Amplex UltraRed (Invitrogen) was added to 20 µL of sample diluted in DPBS in a black 96-well assay plate (Costar). The plate was allowed to incubate for 30 minutes at room temperature, and then read for fluorescence by plate reader (ex/em 535/590 nm).

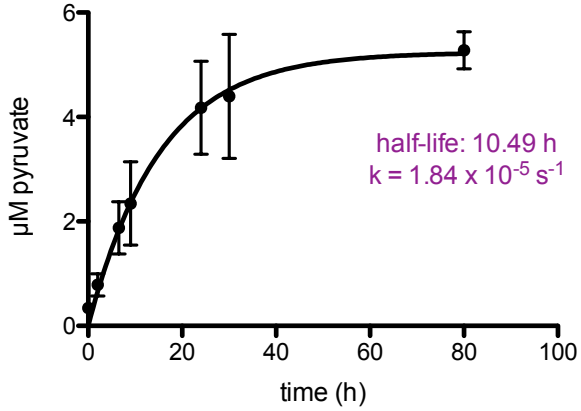


Figure S11. Pyruvate formation from LLV-(MG-I3)-YTKKV shown by enzymatic detection. Pyruvate concentration was determined by using a standard curve.

DETERMINATION OF pK_a VIA NMR TITRATION.

For each case indicated in Table 2, the MG-H TFA salt was dissolved in D_2O at a concentration of ~10 mM with a small amount of acetone as a reference in a 5 mm NMR tube. Either TFA or KOD was then added to adjust the solution to a desired pH read by a Beckman 240 pH meter. ^1H NMR was immediately acquired, and the chemical shift of the hydroimidazolone ring α-H (referenced to acetone) was plotted against pH to produce a titration curve whose equivalence point was determined using GraphPad Prism.

MG-H1

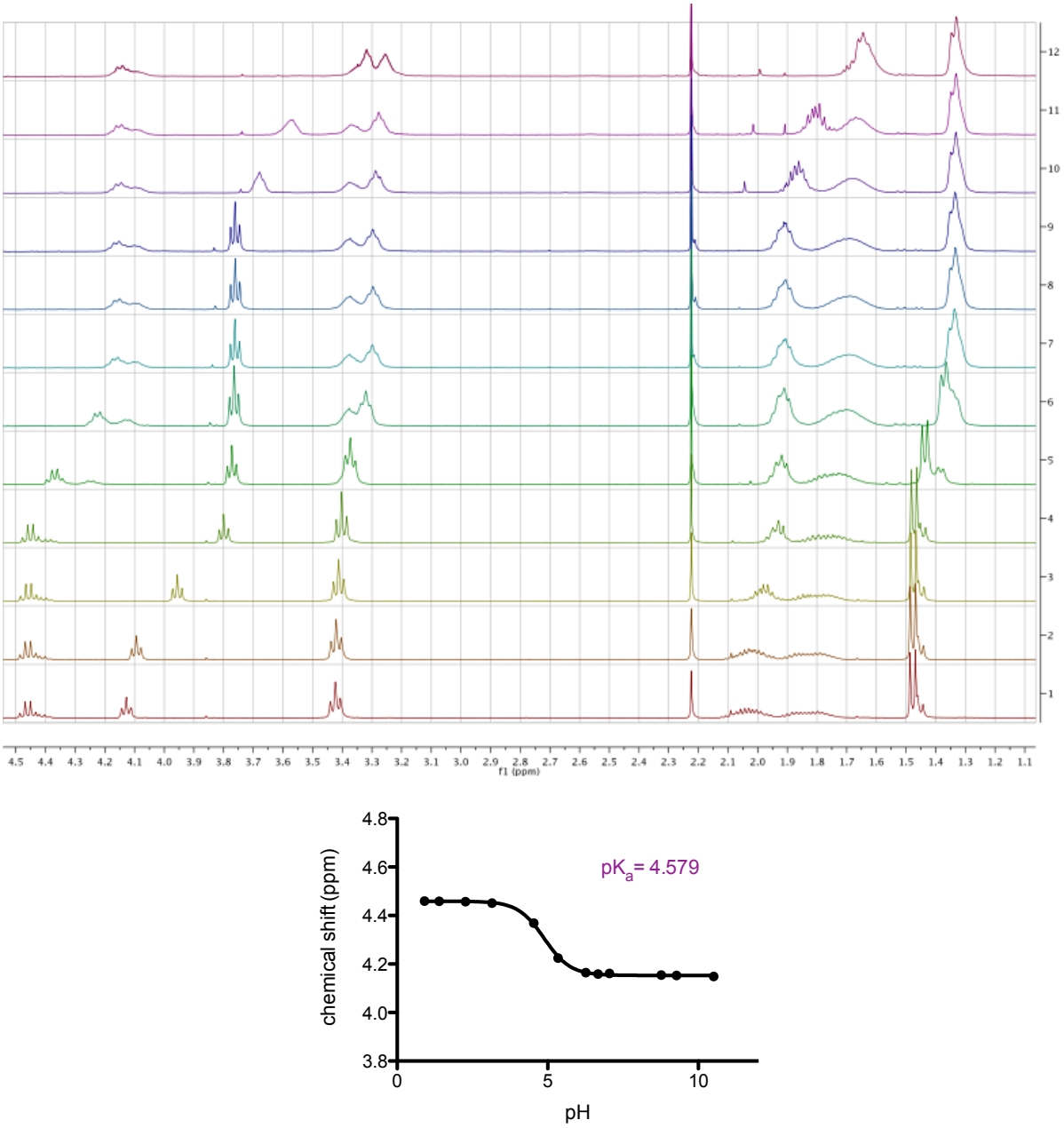


Figure S12. NMR titration of MG-H1 amino acid.

MG-H2

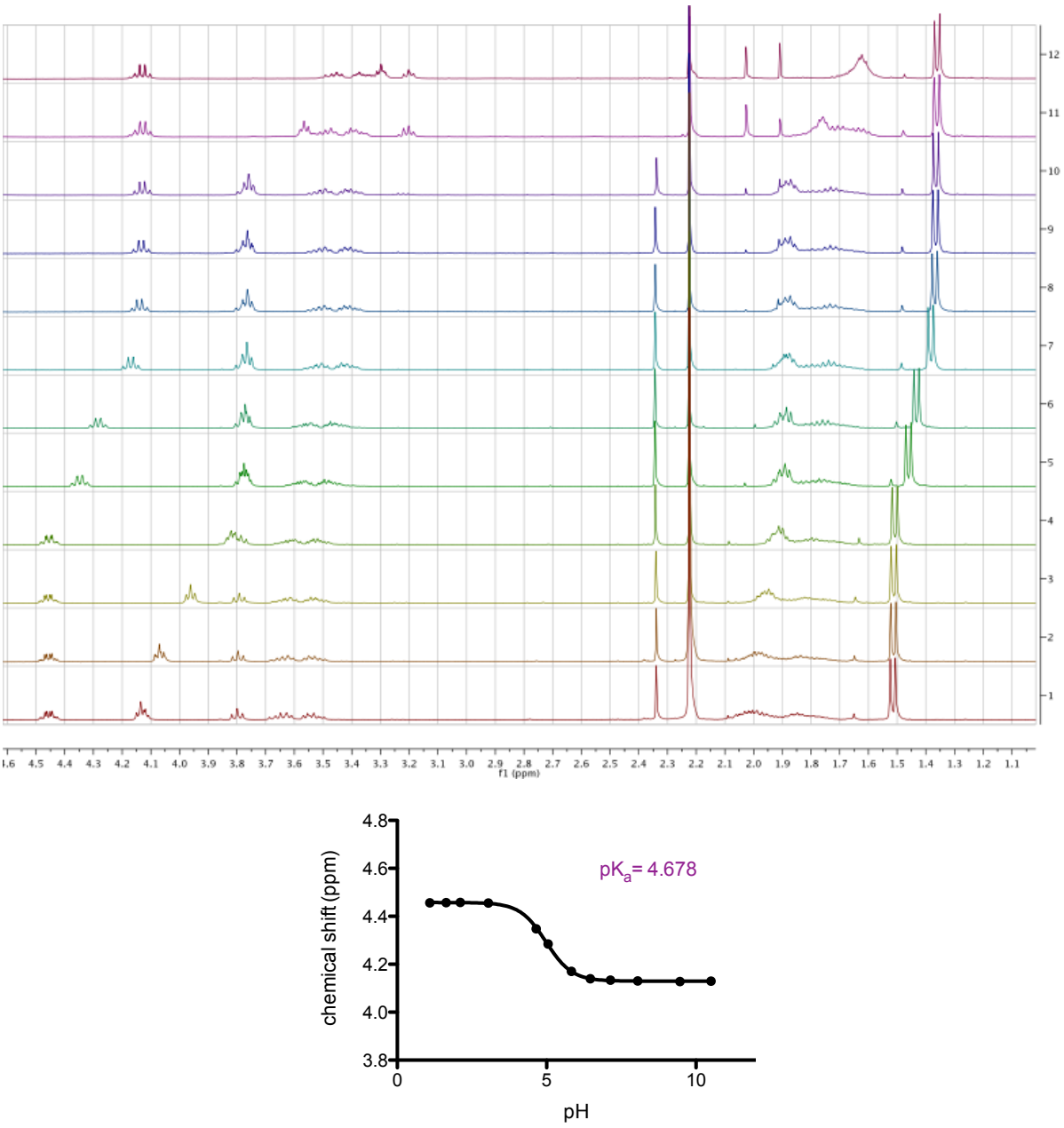


Figure S13. NMR titration of MG-H2 amino acid.

MG-H3

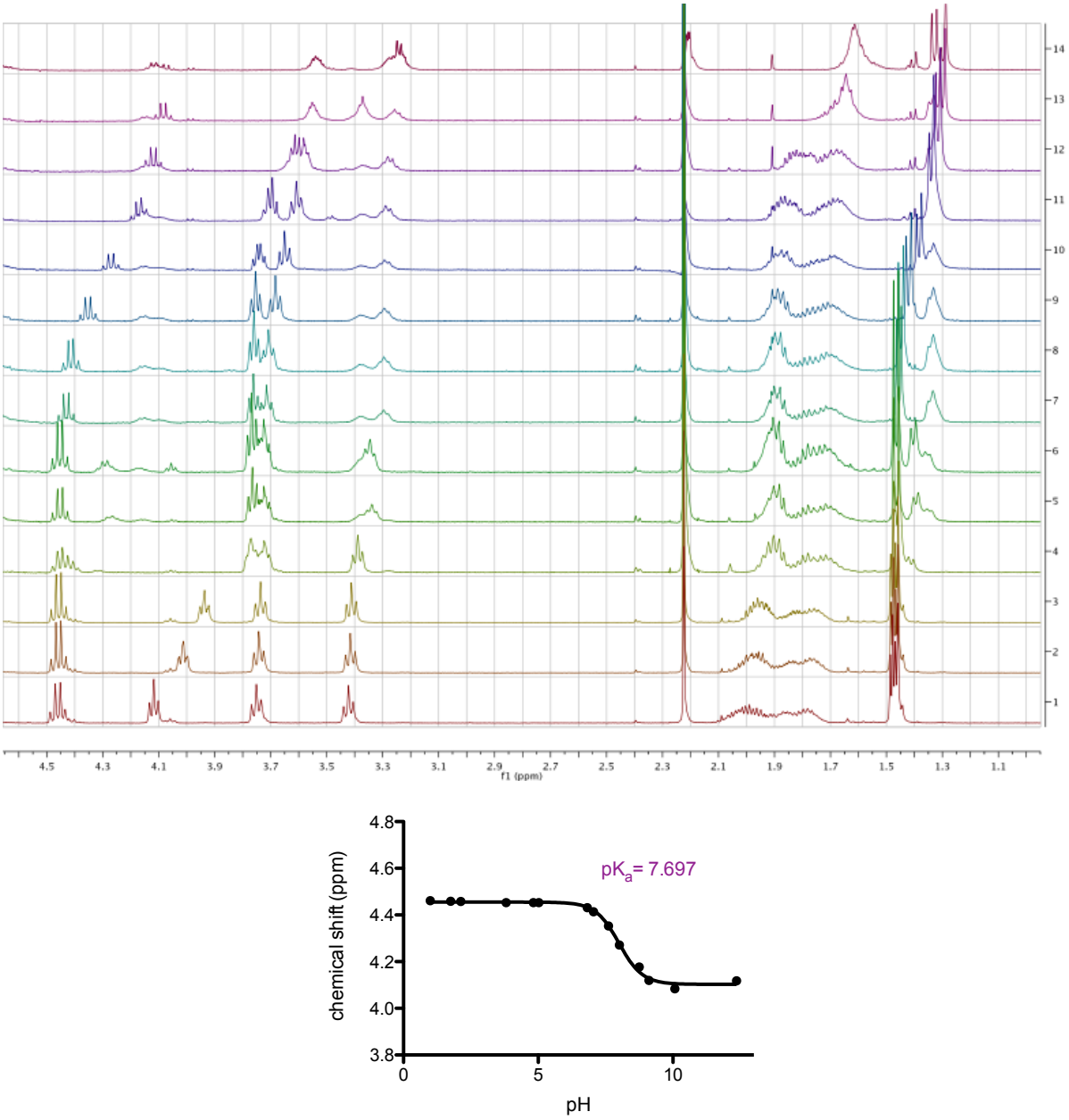


Figure S14. NMR titration of MG-H3 amino acid.

PROTON/DEUTERIUM KINETIC ISOTOPE EFFECT.

Peptide **29** deuterated at the methine position was obtained by incubating the formate salt in D_2O for one week. Deuterium exchange was confirmed by LCMS (HR-MS: $(M+1)^+$ = 1174.6666). For DPPH quenching, 100 µL of a 0.43 mM proto- or deutero-peptide **29** stock solution in H_2O or D_2O, respectively, was added to 100 µL of 0.1 mg/mL DPPH in ethanol. Absorbance at 515 nm was immediately read by plate reader at 1-minute intervals for one hour at room temperature. For MTT reduction, 95 µL of a 1 mg/mL aqueous solution of MTT was added to 5 µL of a 0.43 mM proto- or deutero-peptide **31** stock solution in H_2O or D_2O, respectively, in a glass 96 well

plate. To this, 100 µL of DMSO was added, and the solution was mixed by gently pipetting up and down. The plate was covered and incubated at 37ºC with shaking at 300 RPM. Absorbance at 570 nm was measured by plate reader at various times, as indicated below.

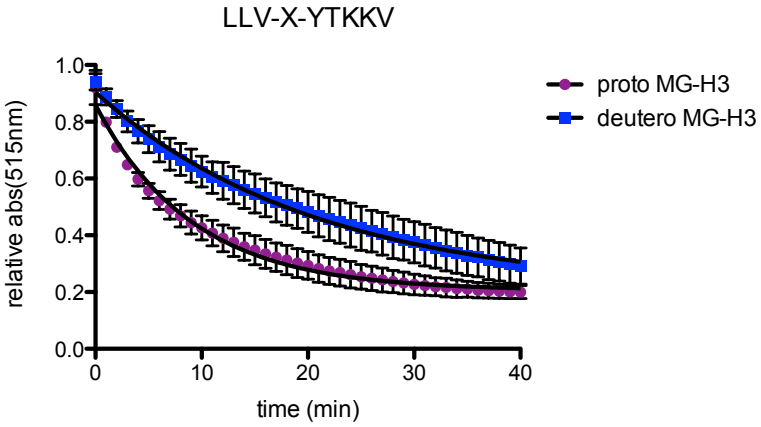


Figure S15. DPPH scavenging by **29** incorporated with either proto- or deutero- MG-H3.

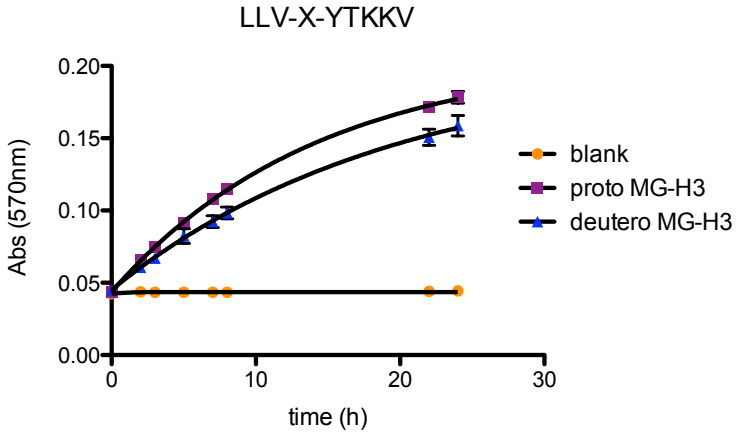


Figure S16. MTT reduction by **29** incorporated with either proto- or deutero- MG-H3.

CELLULAR OXIDATIVE STRESS EXPERIMENTS.

Cell culture

RAW 264.7 macrophages (ATCC) were cultured in Dulbecco's Modified Eagle Medium (DMEM) supplemented with 10% FBS. Cells were grown on petri dishes and passaged every 2-3 days at a ratio of 1:4. For oxidative stress experiments, cells were seeded overnight in 96 well plates at a concentration of 5 x 10^5 /mL in DMEM containing 1% FBS.

DHR123 oxidative stress assay

Cellular oxidative stress was assayed using a well-established protocol.[13] RAW 264.7 macrophages grown overnight were loaded with 5 μM dihydrorhodamine 123 (Invitrogen, 5 mM stock solution in DMSO) in 1% FBS DMEM (200 μL/well) for 1 hour at 37°C. The loading media was then removed, and the cells were washed twice with PBS. 150 μL of fresh 1% FBS DMEM was then added to each well, along with test substrates. Finally, a solution of 4 mM H_2O_2 in PBS was added to the wells to give the appropriate final concentration. The plate was then incubated at 37°C before rhodamine 123 fluorescence was read by plate reader.

Cell permeability of MG-H peptides

Peptides **26-29**, derivatized with a biotin linker (10 μM), were incubated with 10^6 RAW 264.7 macrophages in 1% FBS DMEM (1 mL) for 3 h at 37°C. As a positive control, cells were incubated with 10 μM of biotinylated CyLop-1, a known cell-penetrating peptide.[14] Cells were then washed twice with ice-cold PBS, then gently fixed with 0.25% paraformaldehyde in PBS for 30 min at 4°C. Cells were then pelleted, and the supernatant removed. To permeablize membranes, pellets were resuspended in 0.5% TWEEN-20 in PBS and incubated at 37°C for 15 minutes. The cells were then incubated with a 1:1000 of a 1 mg/mL stock of AlexaFluor 647-conjugated streptavidin (Invitrogen) in 0.1% TWEEN-20 PBS for 30 minutes on ice. Cells were washed twice with ice-cold PBS, then resuspended in 500 μL PBS and analyzed by flow cytometry.

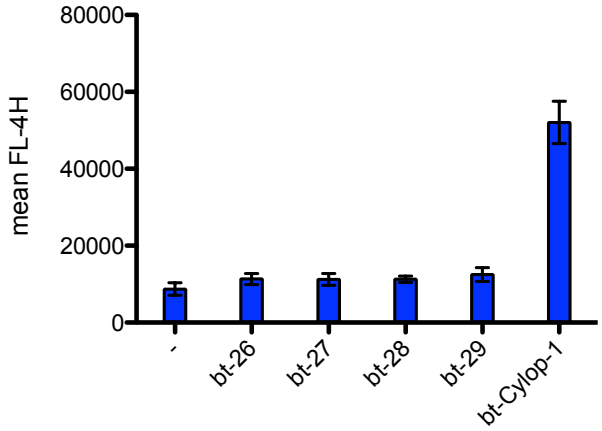


Figure S17. Intracellular incorporation of various biotinylated peptides.

Data analysis and statistical methods

All statistical analysis contained in this manuscript were obtained using standard algorithms contained in the GraphPad Prism software package. For cellular antioxidant assays, the mean background fluorescence value for each 96-well plate, determined from control conditions containing cells, fluorophore, and H_2O_2 (when indicated), was first subtracted from each raw data value. Data was then normalized on a scale from 0 to 100 with respect to the mean maximum fluorescence value for each plate, determined from control wells containing the highest H_2O_2 concentration employed in experiments. Thus, for experiments reported in panels A and B of Figure S18, respectively, maximum values were obtained from conditions employing

160 and 80 μM H_2O_2. A significant amount of variation in the absolute values of raw data was observed in experiments conducted in different 96-well plates or on different days (all experimental trends were reproduced on at least two separate occasions); background-subtracted, normalized data was therefore first subjected to analysis of covariance (ANCOVA) procedure to determine the suitability of combining data sets. Thus, linear regressions were obtained for scatterplots of processed data as a function of independent concentration variables, and two-tailed P values for these fits were compared to evaluate the null hypothesis that slopes are all identical. These analyses revealed a high degree of inter-experiment consistency for all processed data, which allowed us to pool all data from identical experiments (reported graphically in Figure S18A and B) for subsequent statistical analyses.

To evaluate the effects of experimental variables on H_2O_2-induced cellular fluorescence, pooled data was subjected to another set of multiple regression analyses. For experiments testing the effects of additives at single concentrations (Figure S18A), differences between regression slopes were determined with respect to control conditions lacking additive. Results reported in Figure 2 (left side) represent the differences between slopes of pooled regression lines, and error was calculated from standard error values, an output of regression analyses, using standard equations for propagation of error. Because the concentration of H_2O_2 is fixed for each additive reported in Figure S18B, one would expect linear fits to possess slopes equaling zero for inactive compounds. Thus regression lines from conditions employing MG-H3 conjugate **29** and ascorbic acid were found to possess significant deviations from zero with greater than 95% confidence ($P < 0.0001$ in both cases), and data reported in Figure 2D represents the magnitude of slopes from linear regressions, and standard error values obtained from standard least-squares fitting procedures. Notably, none of the dose-response plots reported in Figure 2D was found to deviate significantly from linearity, as measured by Runs test for linearity implemented in GraphPad Prism software package.

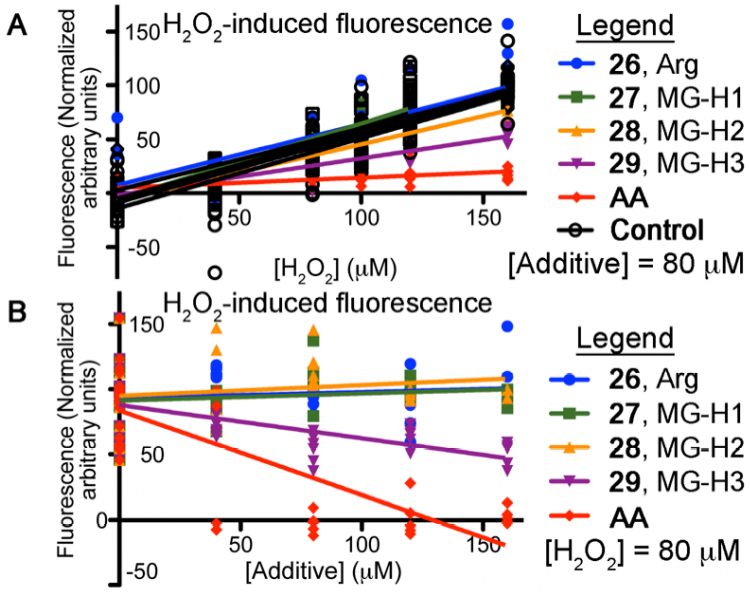


Figure S18. Dose-response of oxidatively-induced cellular fluorescence to (A) various concentrations of oxidant H_2O_2 at fixed levels of additive, or (B) various concentrations of additive at fixed levels of H_2O_2.

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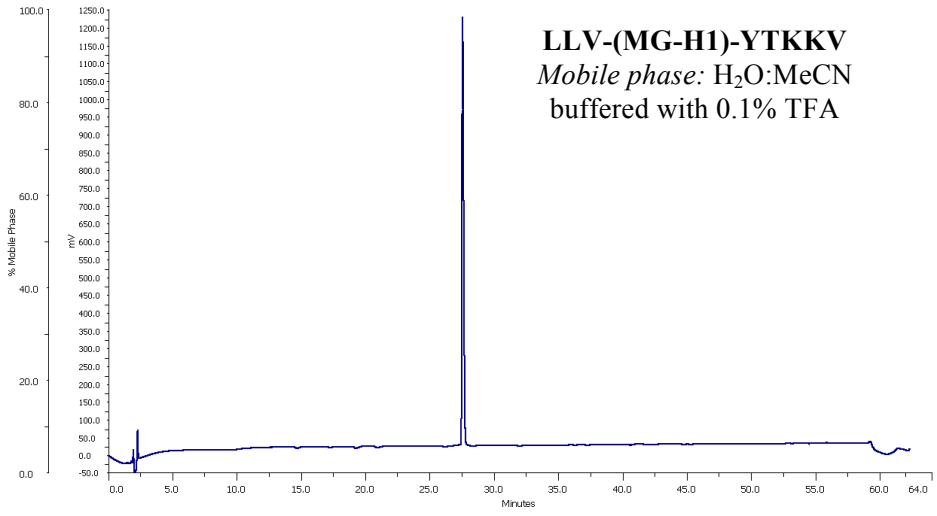
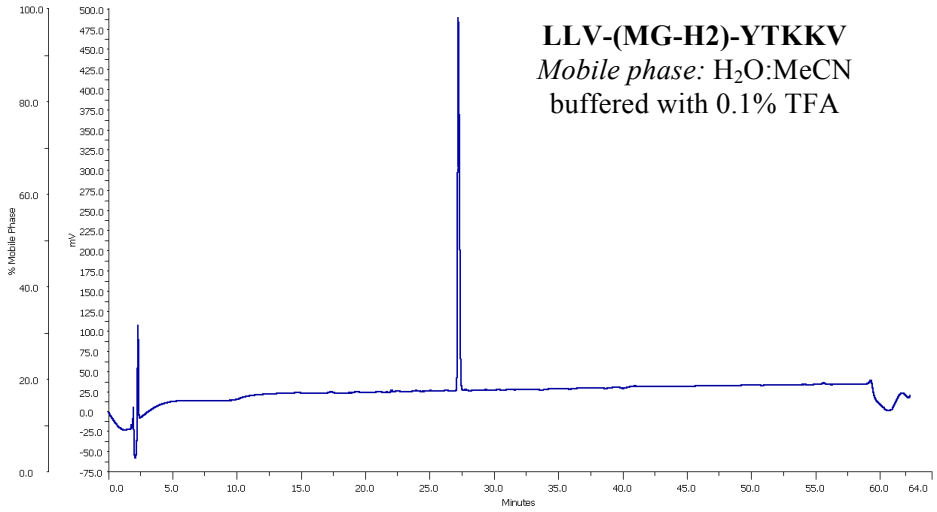
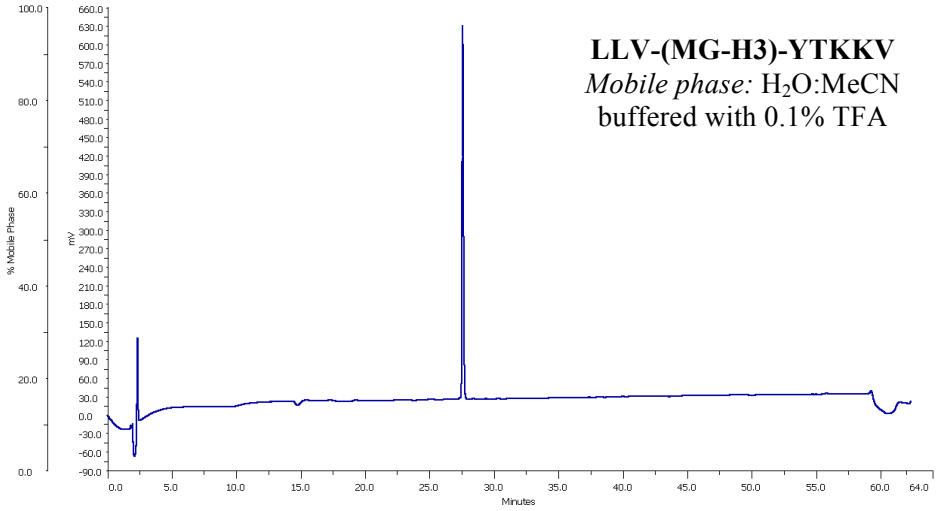
CATALOG OF ANALYTICAL HPLC CHROMATOGRAMS.

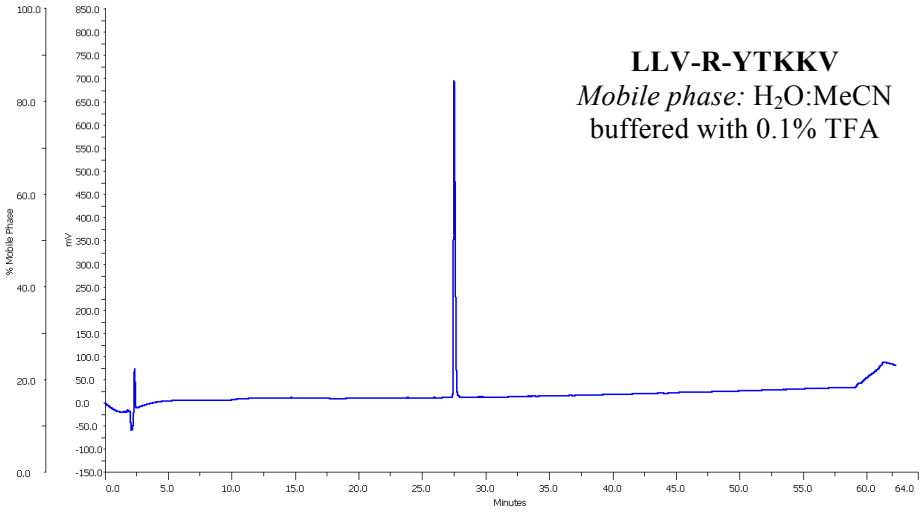




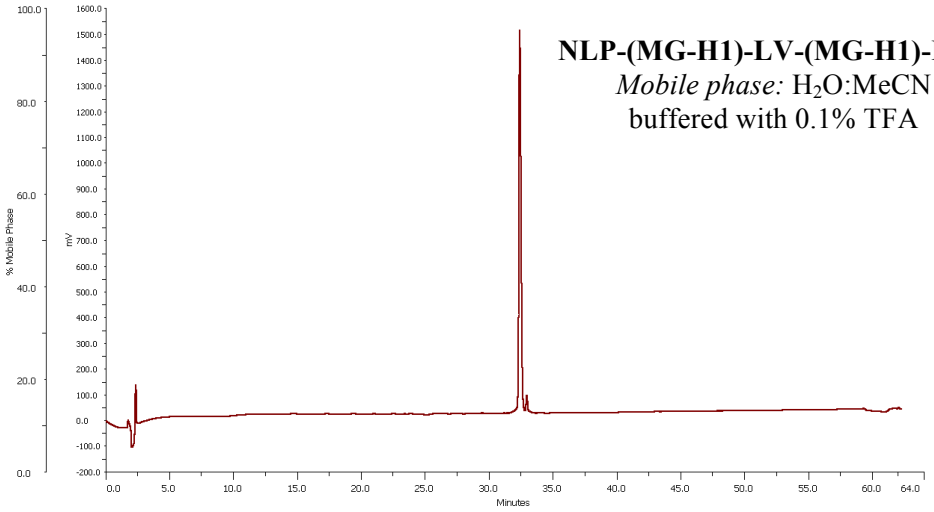
LLV-(MG-H2)-YTKKV
Mobile phase: H_2O:MeCN
buffered with 0.1% TFA



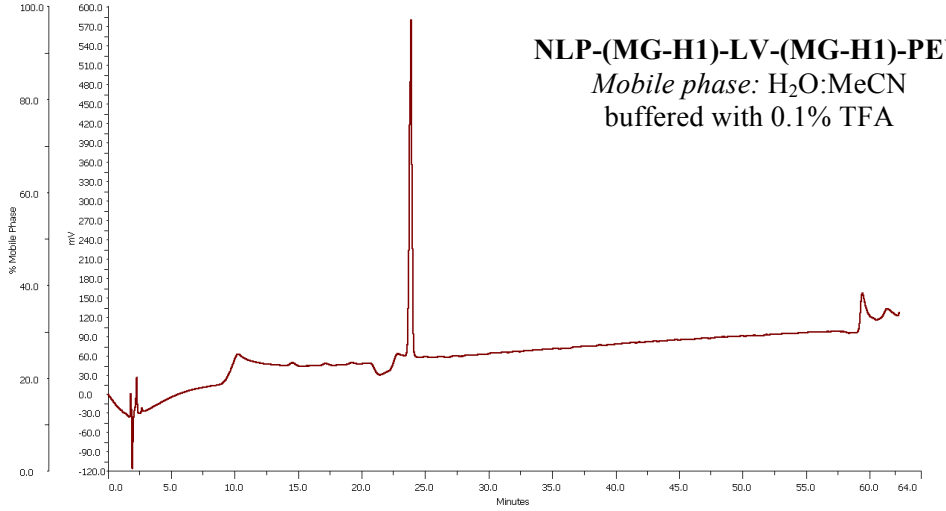
LLV-(MG-H3)-YTKKV
Mobile phase: H_2O:MeCN
buffered with 0.1% TFA



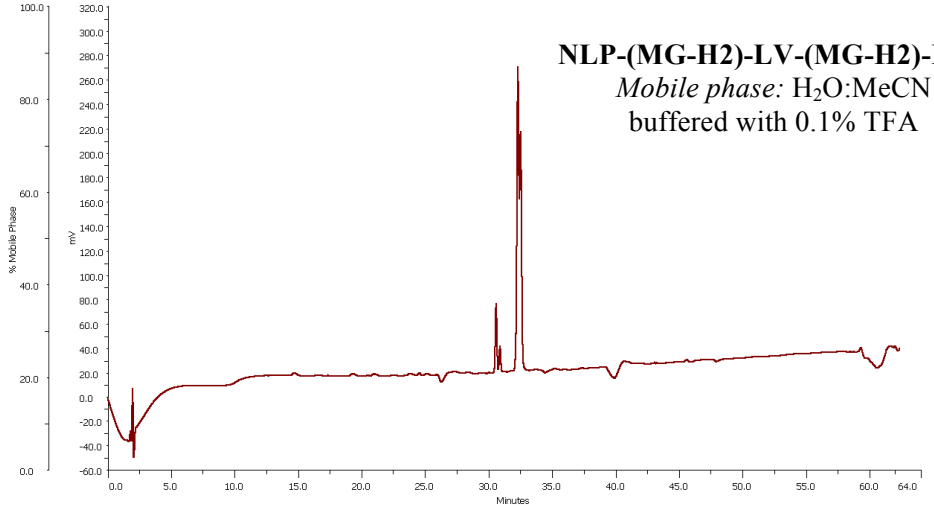
LLV-R-YTKKV
Mobile phase: H_2O:MeCN
buffered with 0.1% TFA



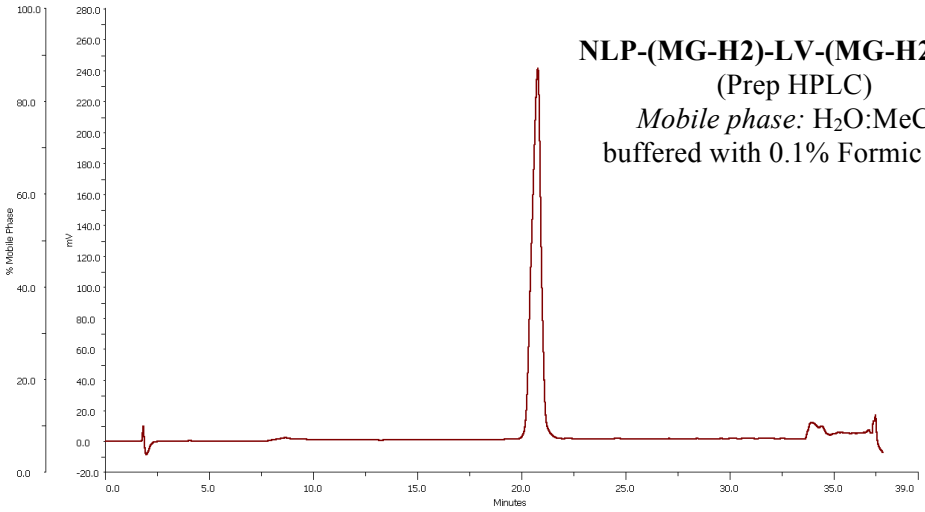
NLP-(MG-H1)-LV-(MG-H1)-PEV
Mobile phase: H_2O:MeCN
buffered with 0.1% TFA



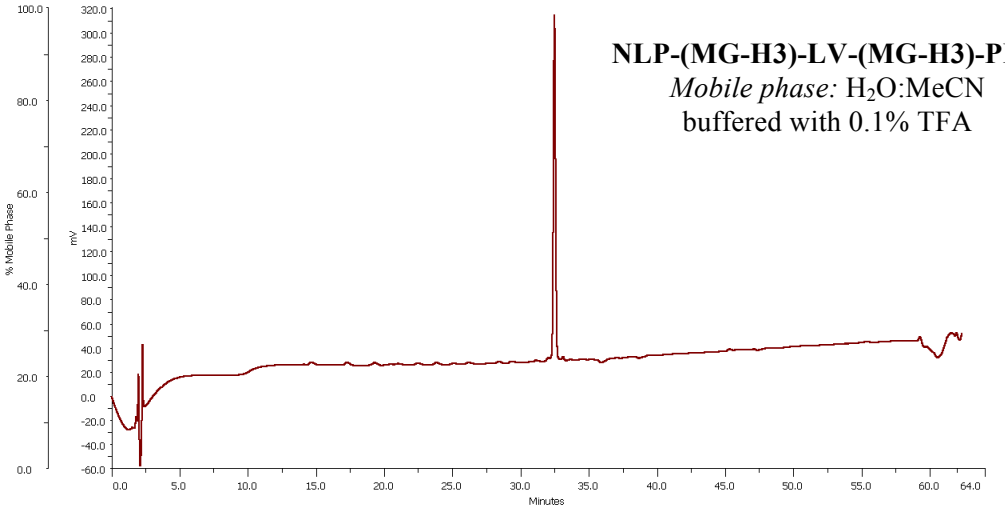
NLP-(MG-H1)-LV-(MG-H1)-PEV
Mobile phase: H_2O:MeCN
buffered with 0.1% TFA



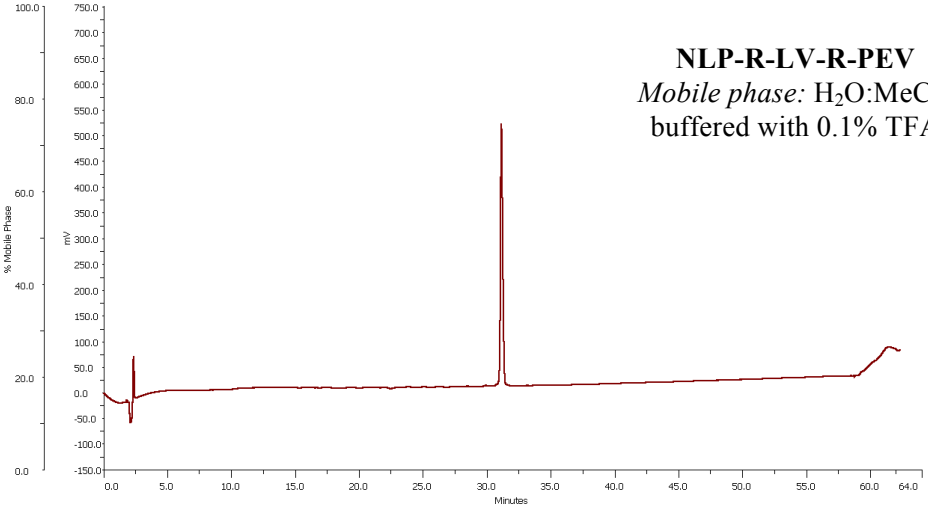
NLP-(MG-H2)-LV-(MG-H2)-PEV
Mobile phase: H_2O:MeCN
buffered with 0.1% TFA



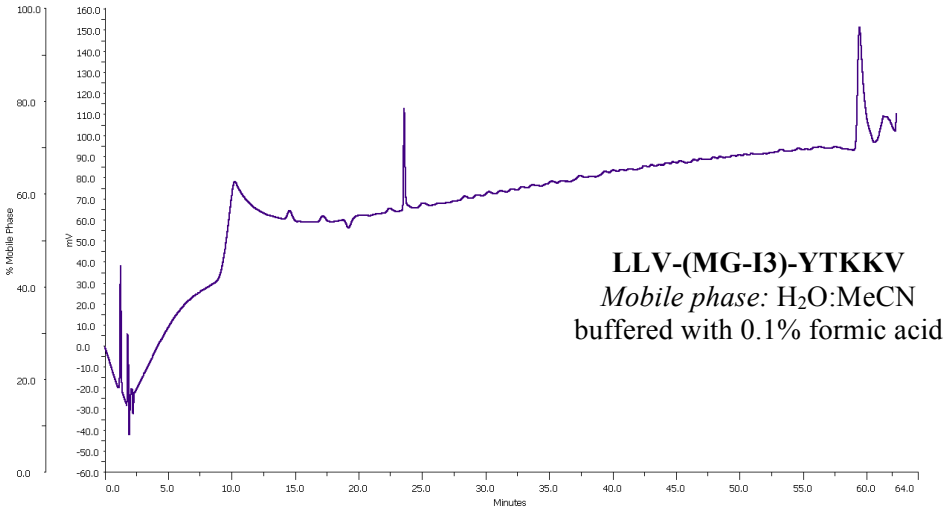
NLP-(MG-H2)-LV-(MG-H2)-PEV
(Prep HPLC)
Mobile phase: H_2O:MeCN
buffered with 0.1% Formic Acid



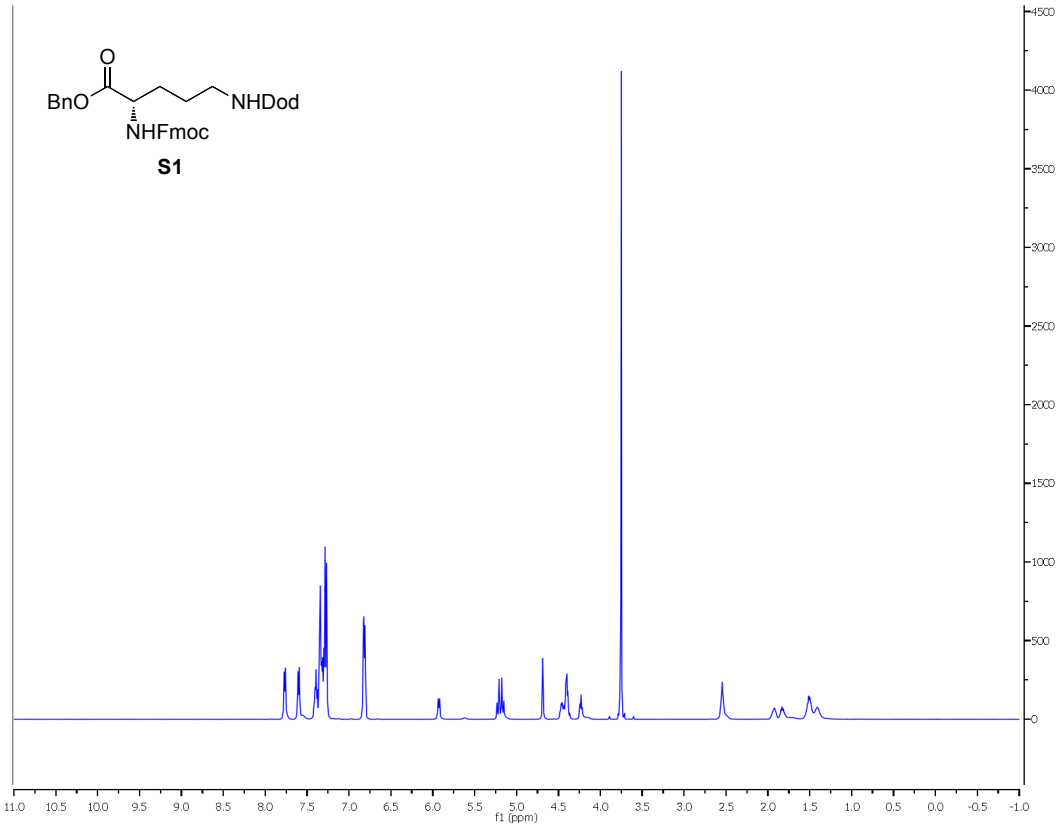
NLP-(MG-H3)-LV-(MG-H3)-PEV
Mobile phase: H_2O:MeCN
buffered with 0.1% TFA

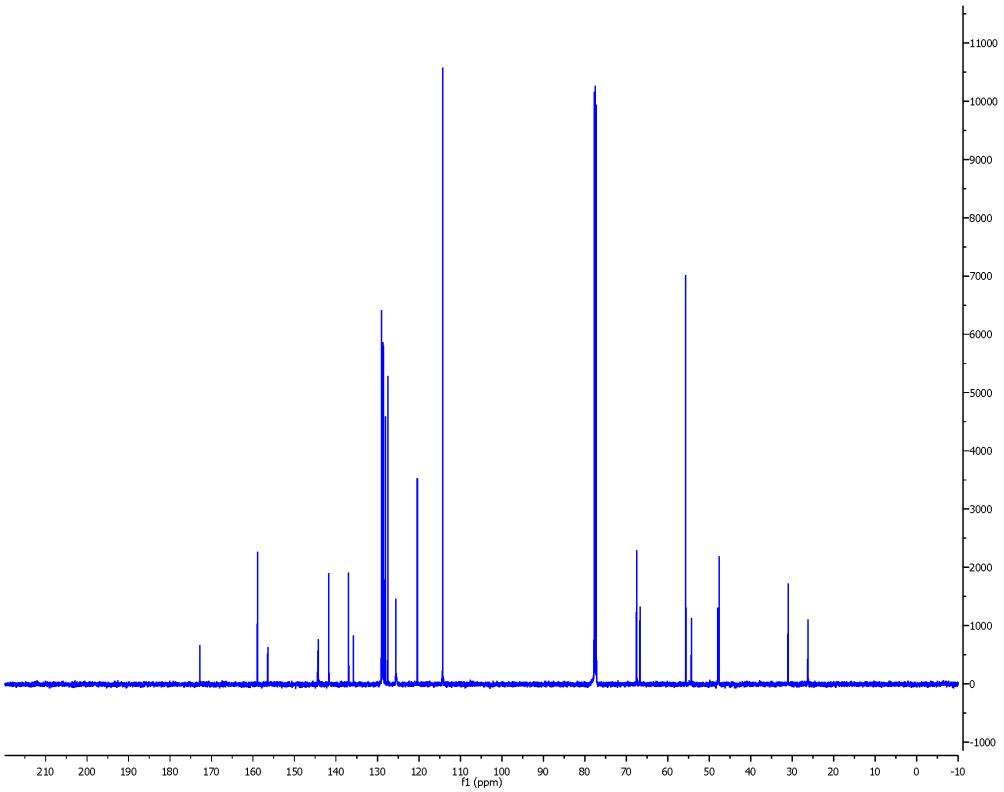


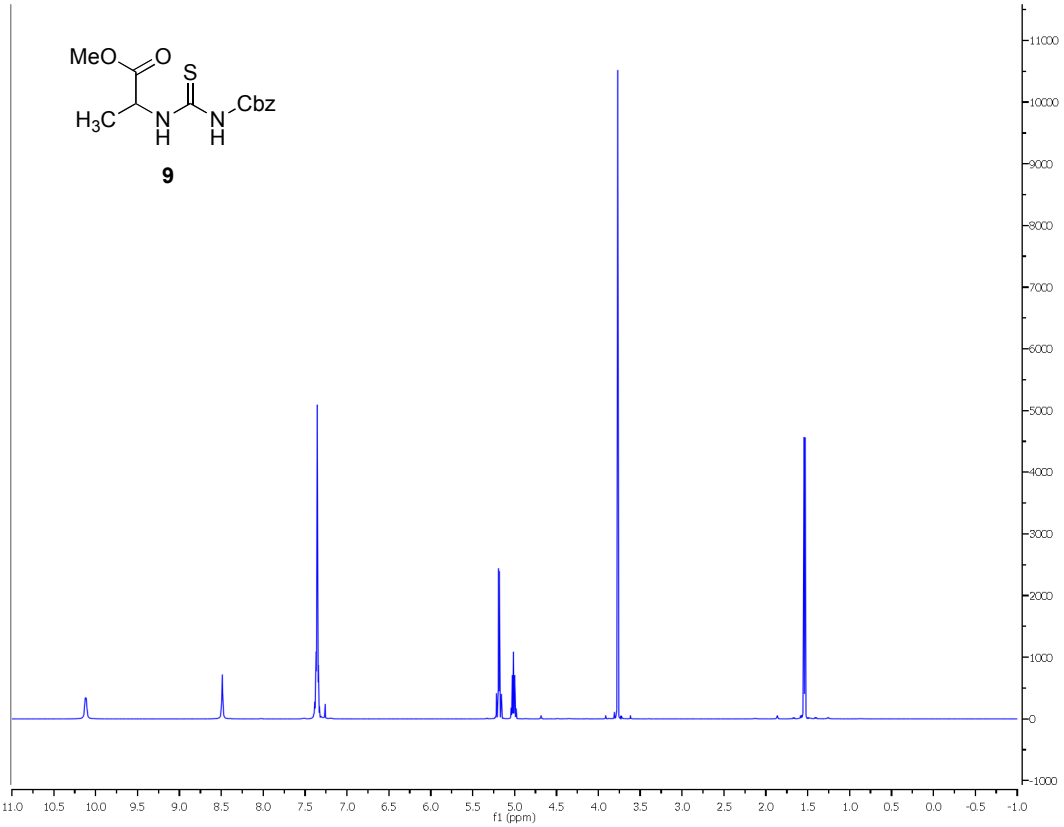
NLP-R-LV-R-PEV
Mobile phase: H_2O:MeCN
buffered with 0.1% TFA



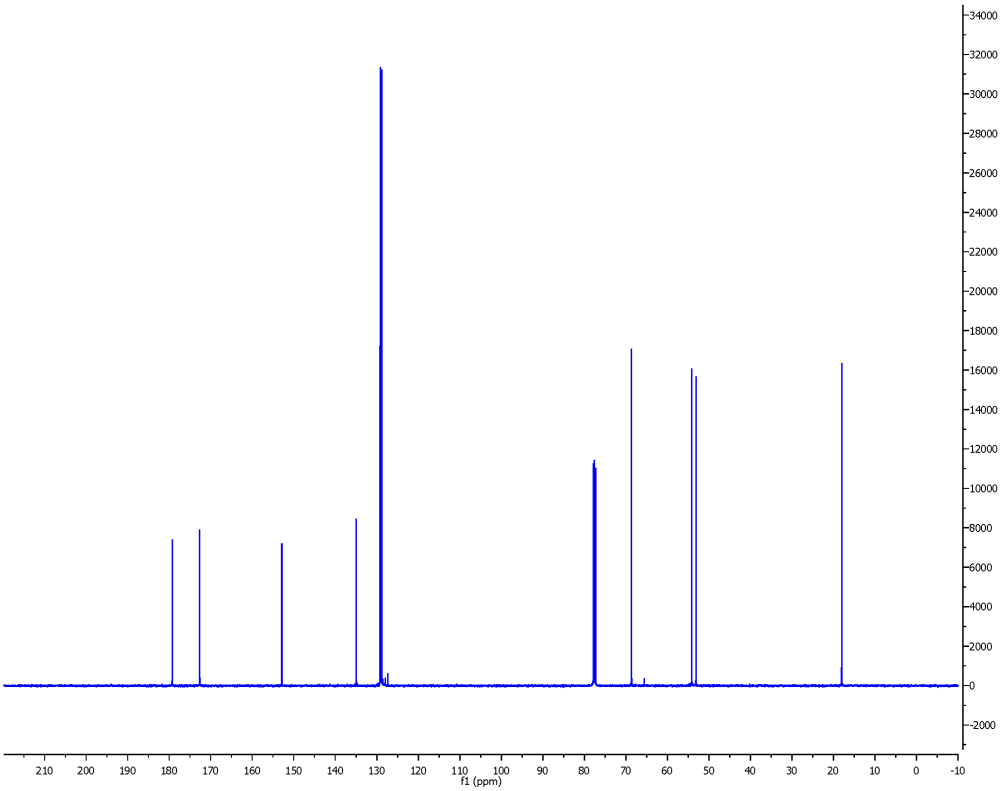
CATALOG OF ^{1}H and ^{13}C NMR SPECTRA

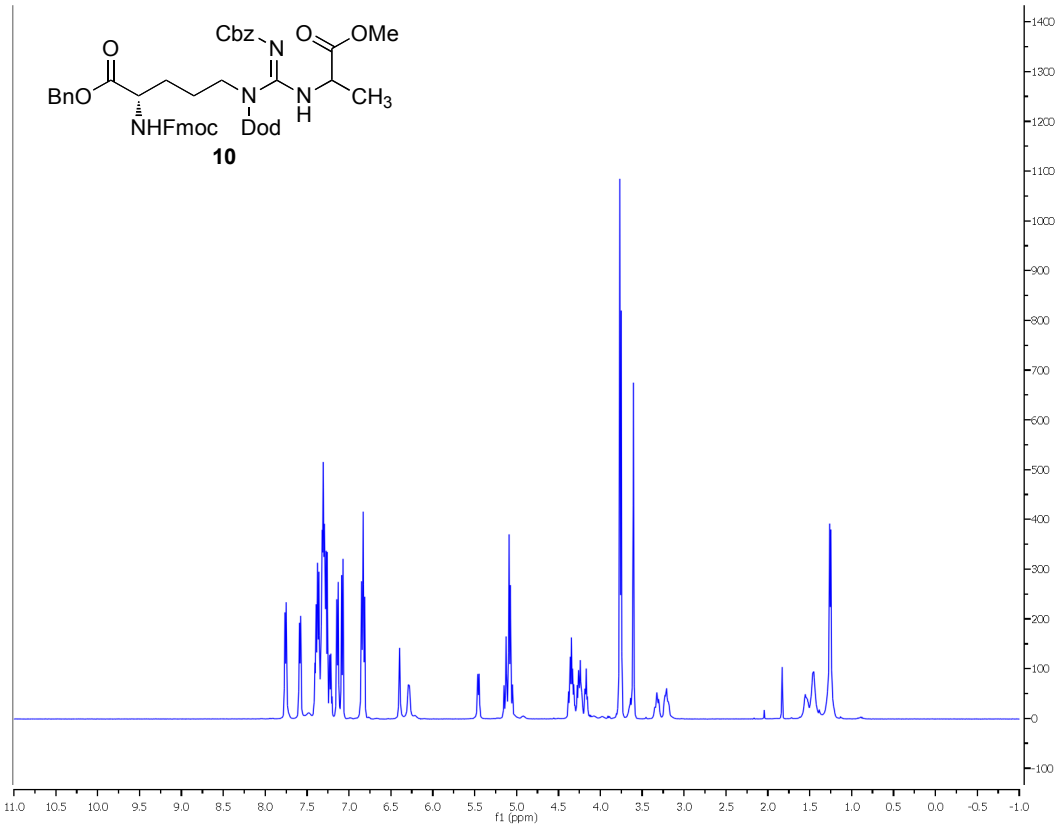


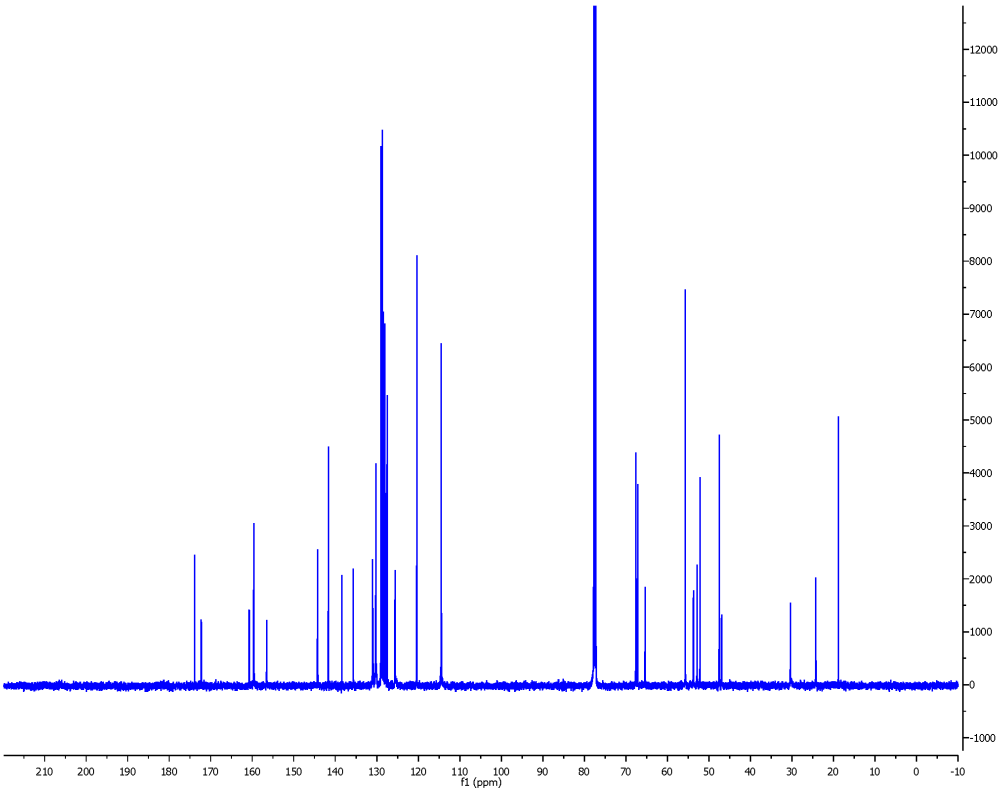

11000
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
-1000
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

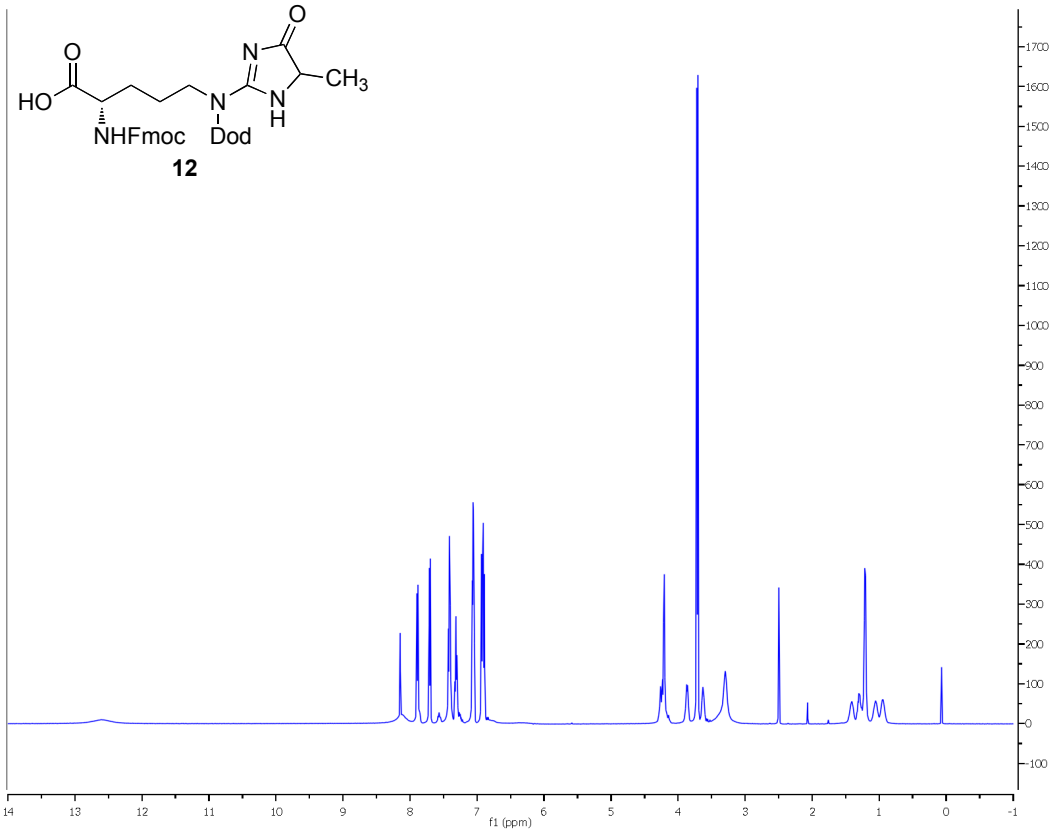

MeO
O
S
H3C
N
H
N
H
Cbz
11000
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
-1000
11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0
f1 (ppm)

9

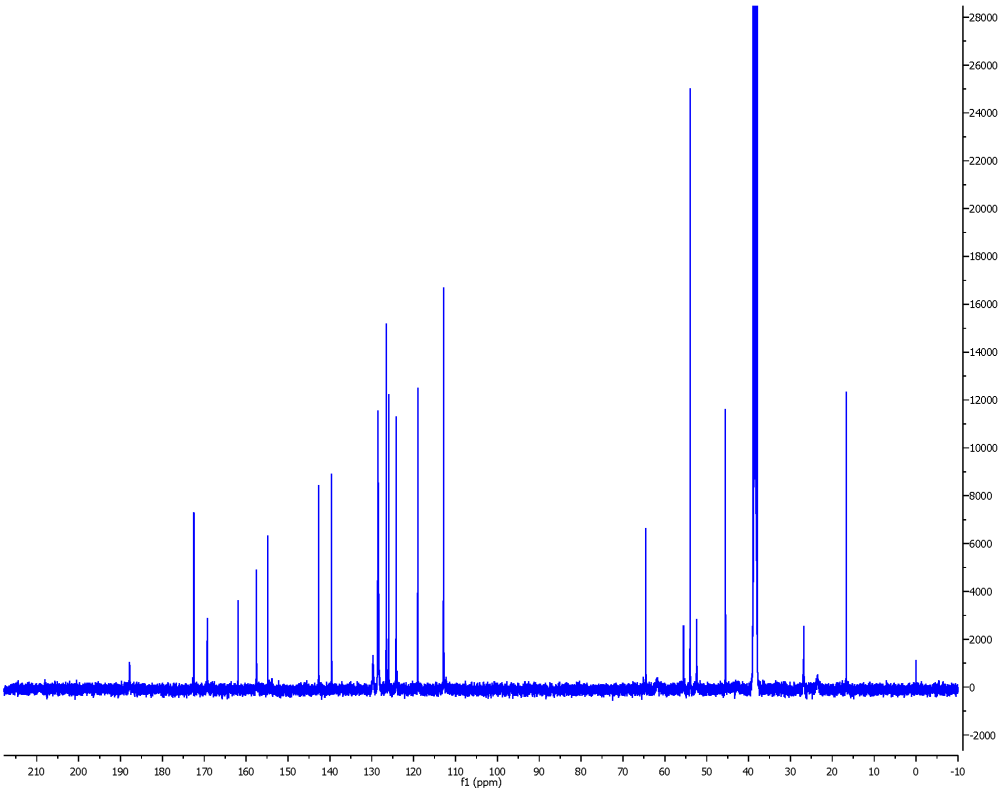

f1 (ppm)

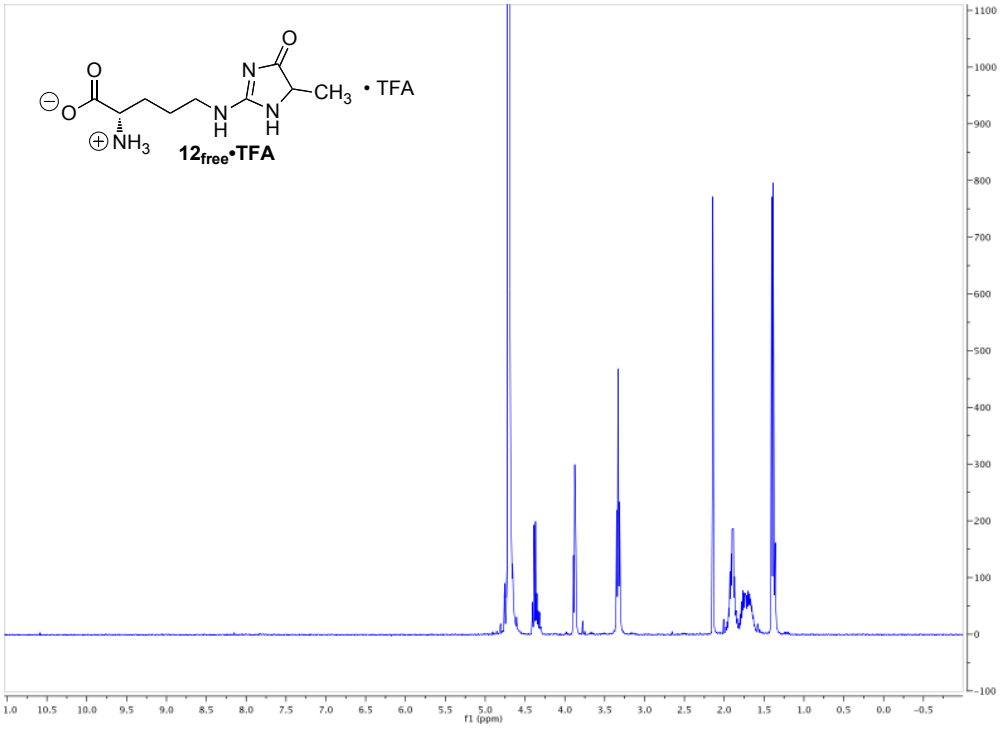

Cbz
N
O
OMe
O
BnO
N
N
H
CH3
NHFmoc
Dod
10
f1 (ppm)

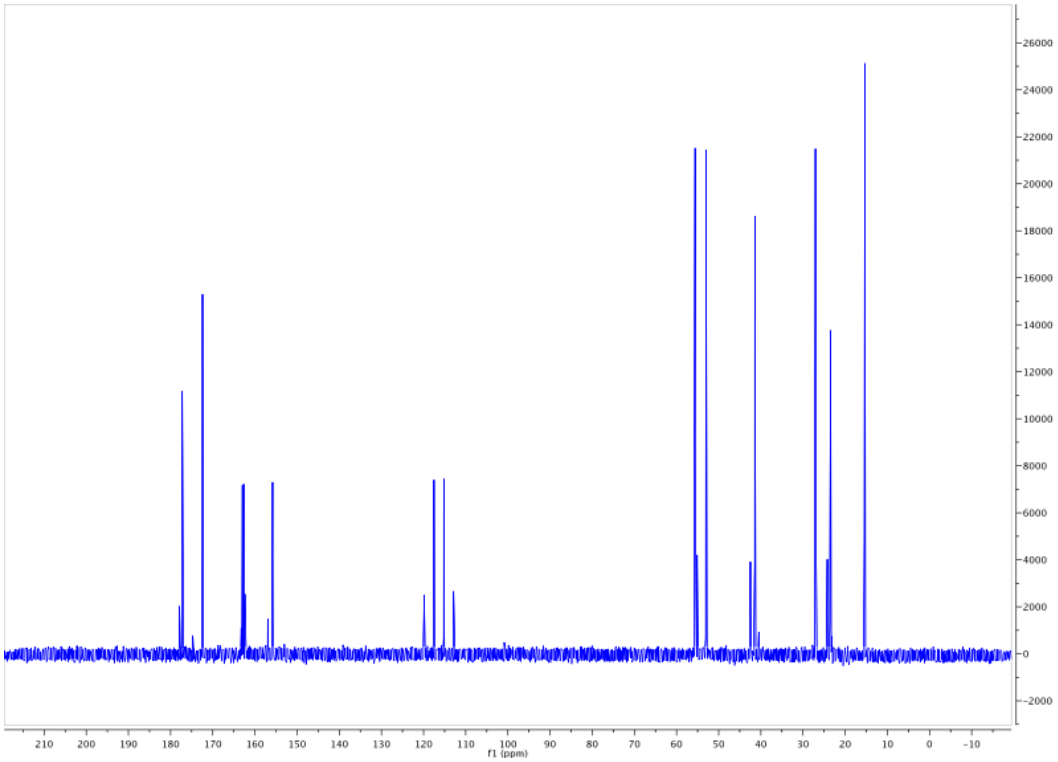


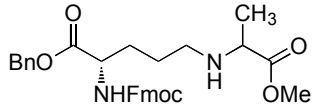


12

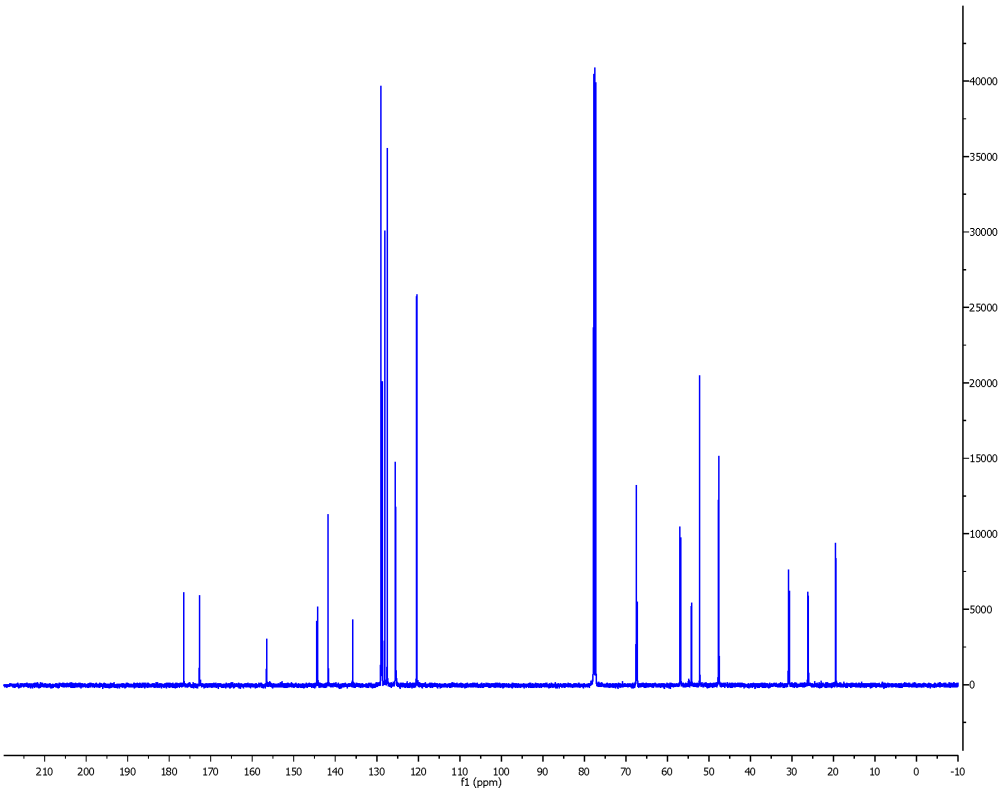

f1 (ppm)

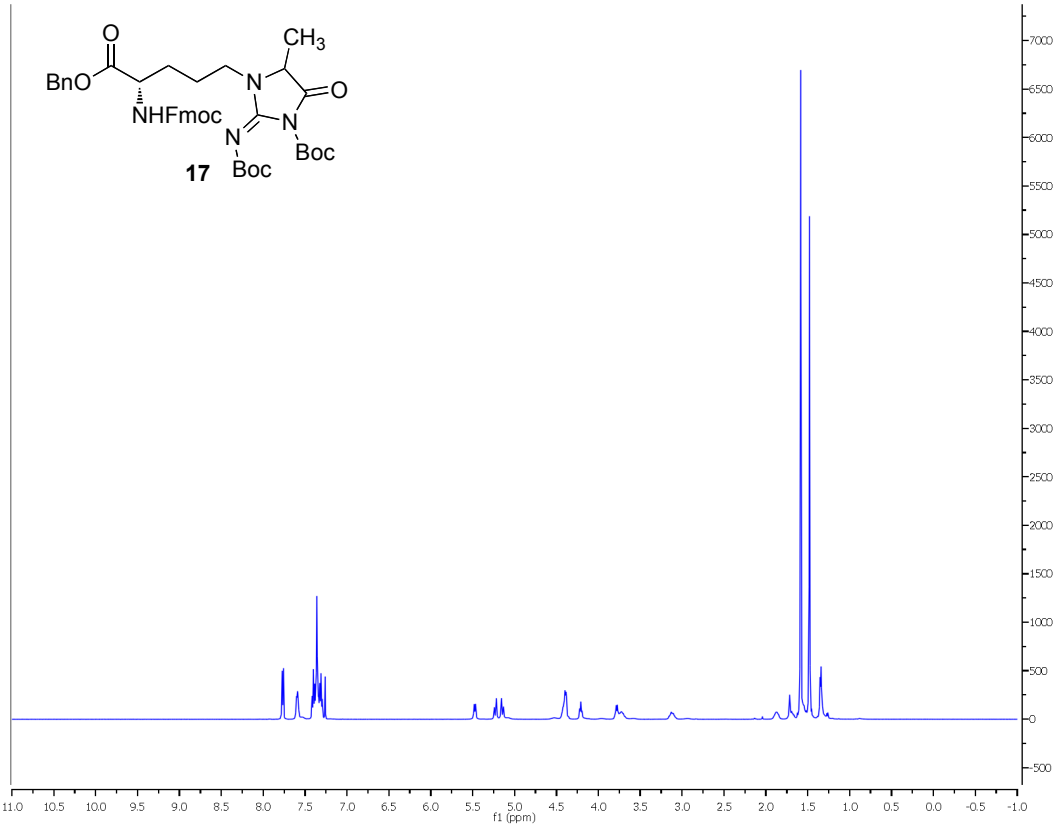

• TFA
12free•TFA
f1 (ppm)



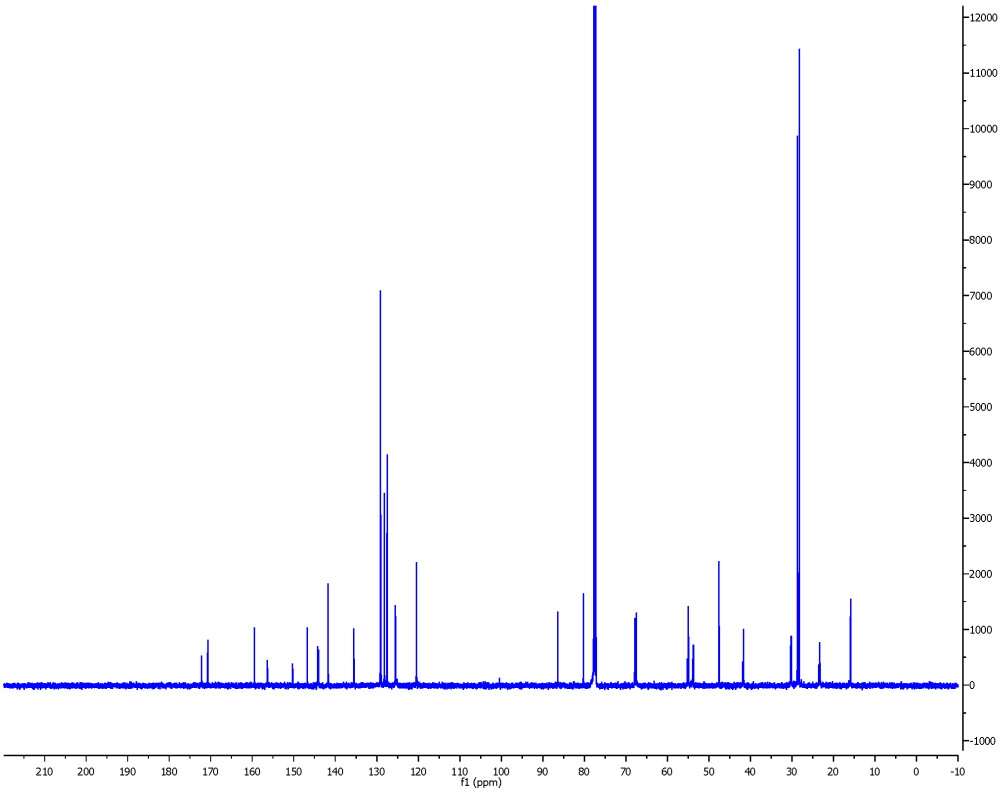


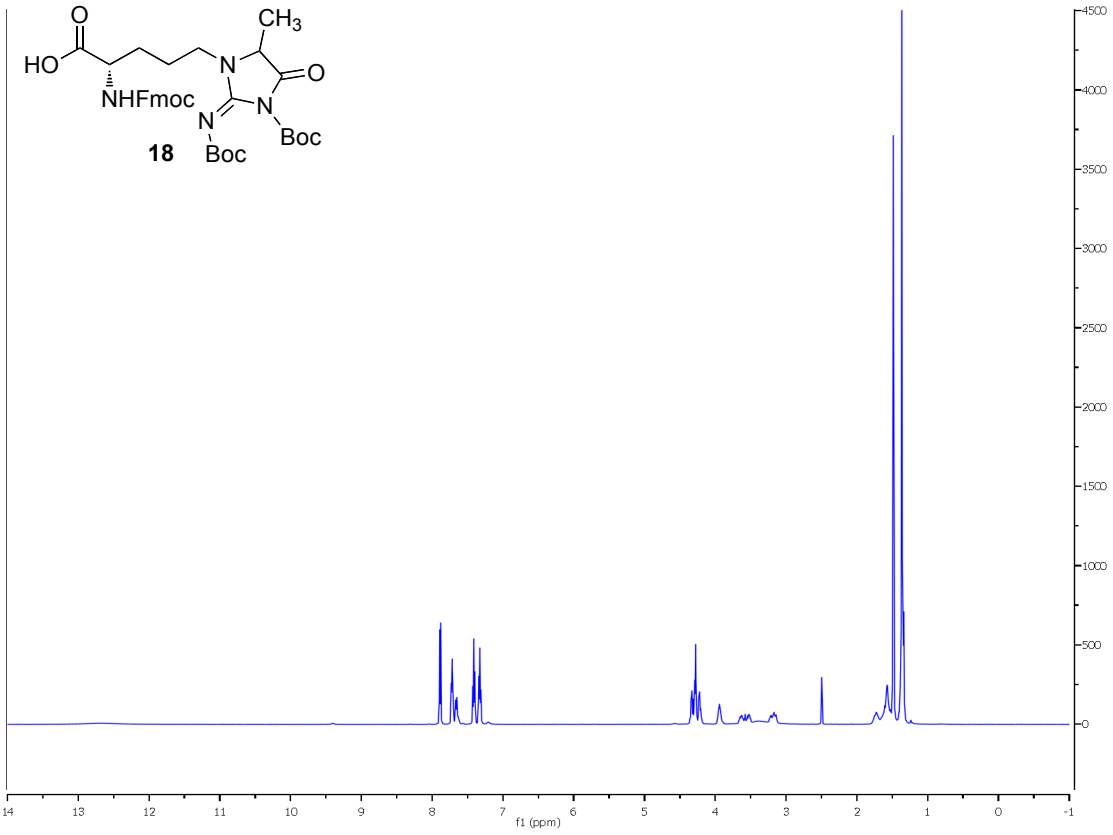
14

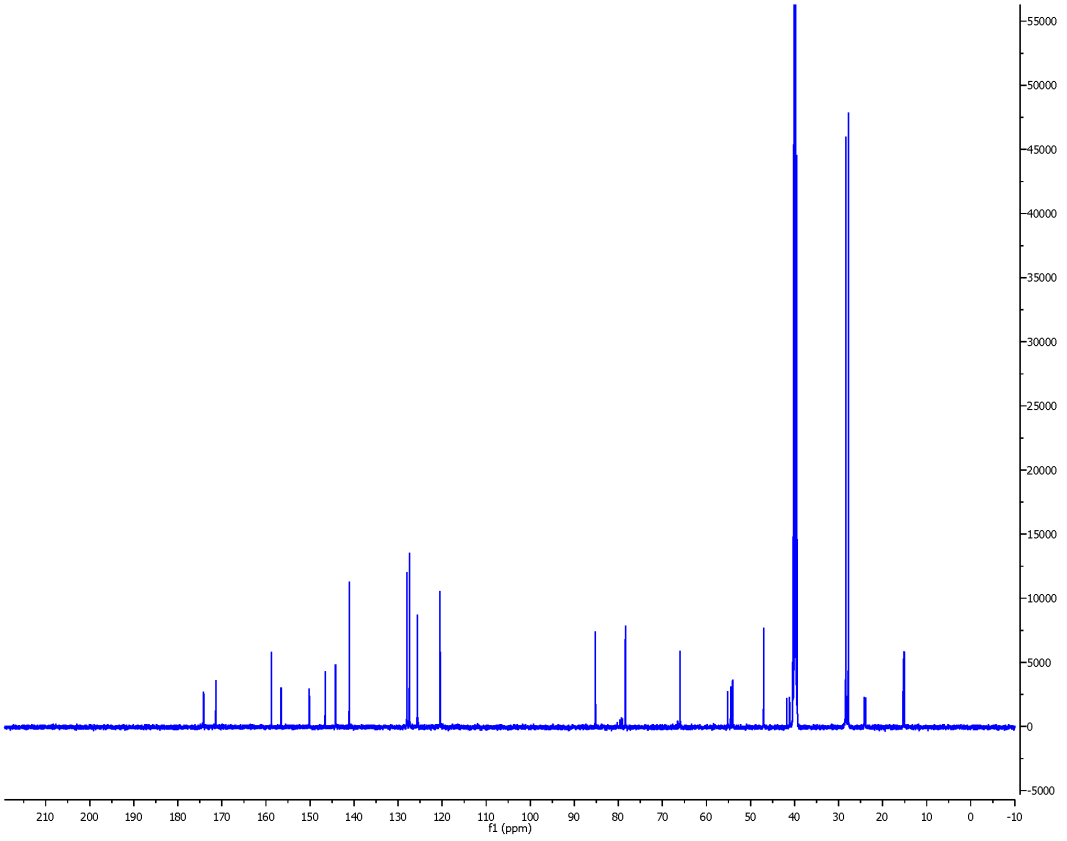

40000
35000
30000
25000
20000
15000
10000
5000
0
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

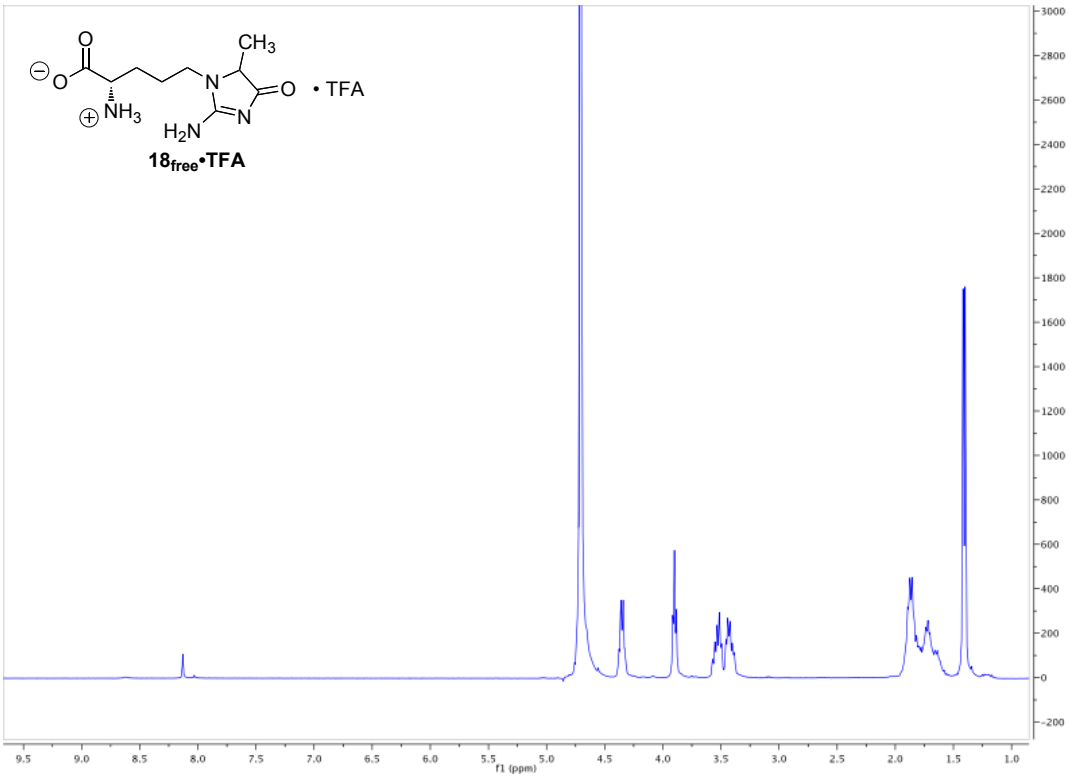

O
BnO
NHFmoc
CH3
N
O
N
N
Boc
Boc
7000
6500
6000
5500
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0
-500
11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0
f1 (ppm)

17

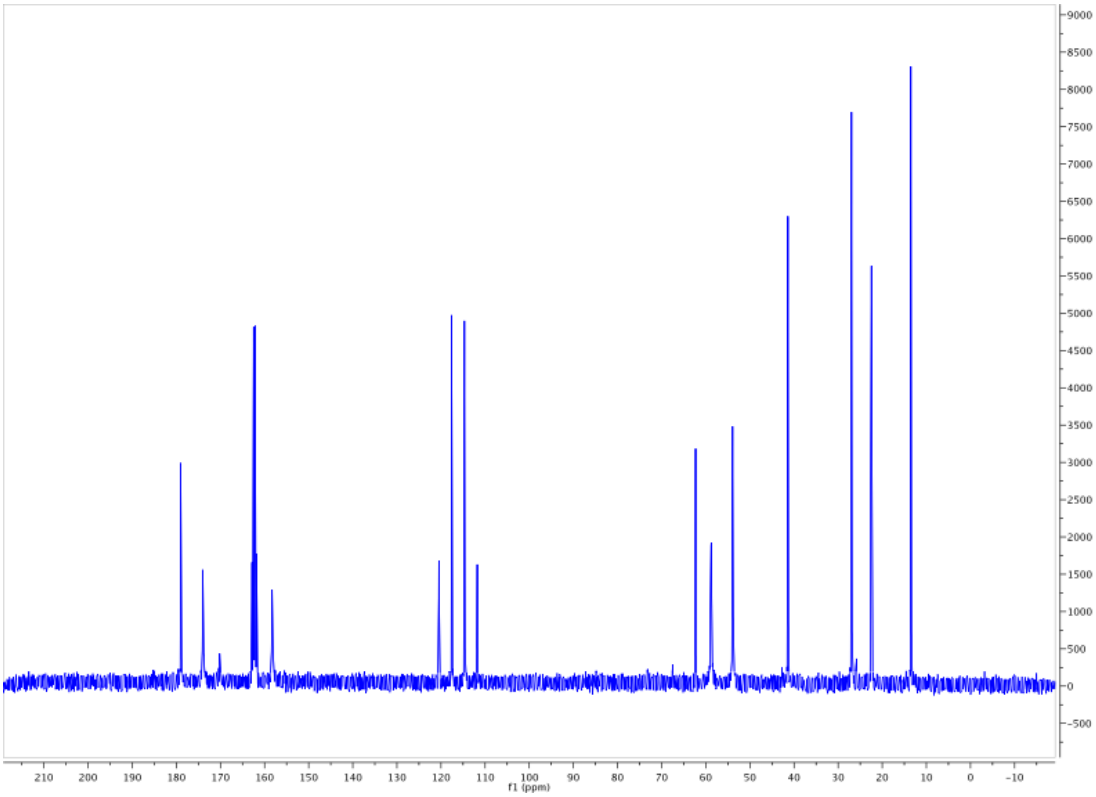

f1 (ppm)

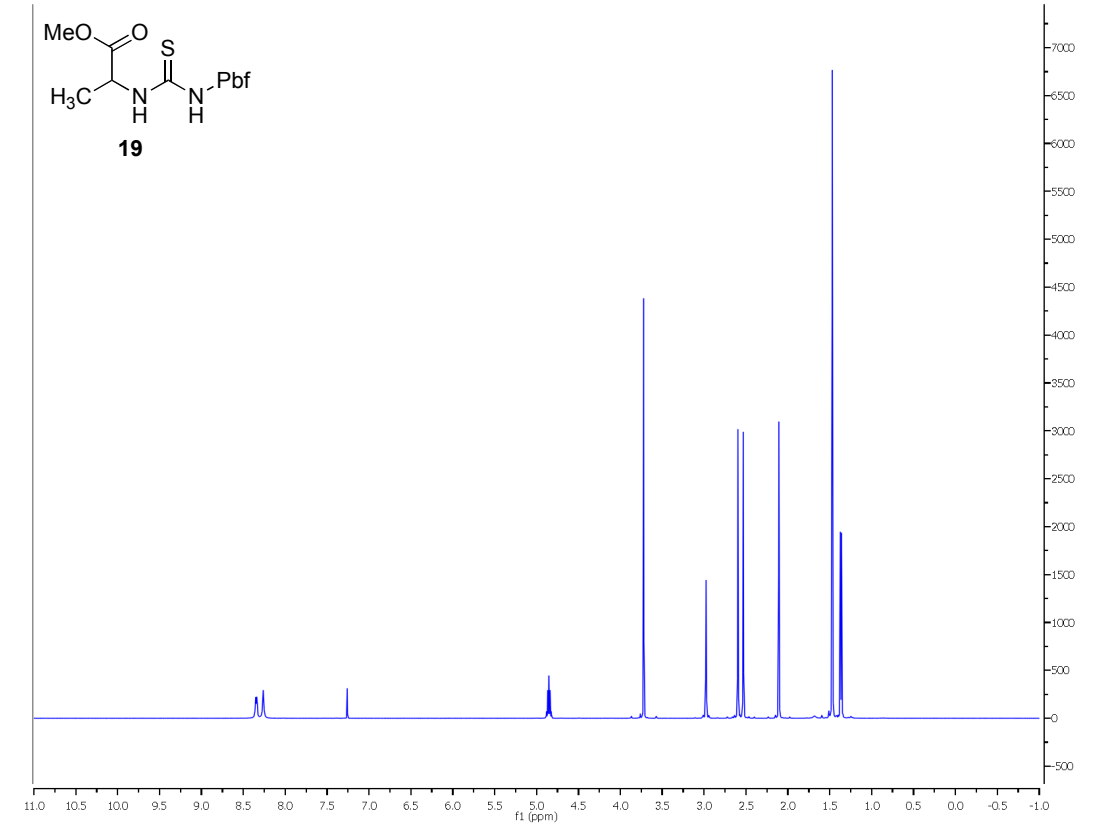

HO
O
NHFmoc
N
N
CH3
O
N
Boc
Boc
18
f1 (ppm)


55000
50000
45000
40000
35000
30000
25000
20000
15000
10000
5000
0
-5000
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

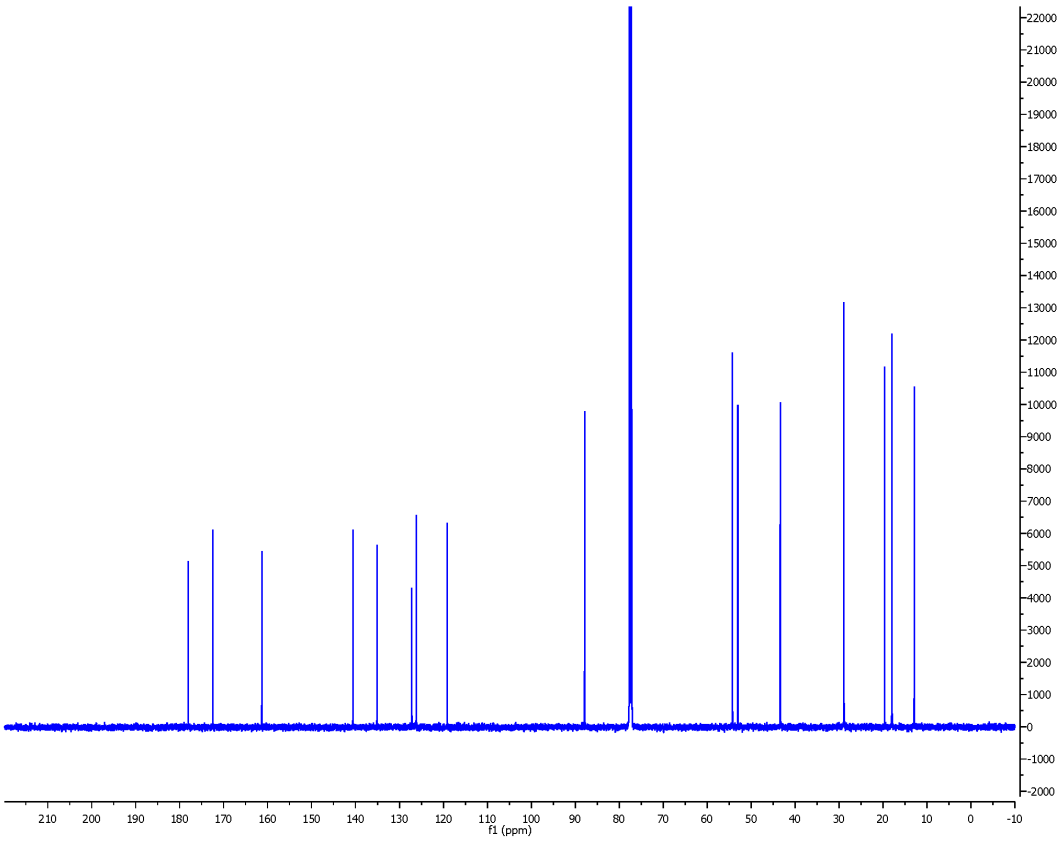

O
O
NH3
CH3
N
O
N
H2N
• TFA
3000
2800
2600
2400
2200
2000
1800
1600
1400
1200
1000
800
600
400
200
0
-200
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0
f1 (ppm)

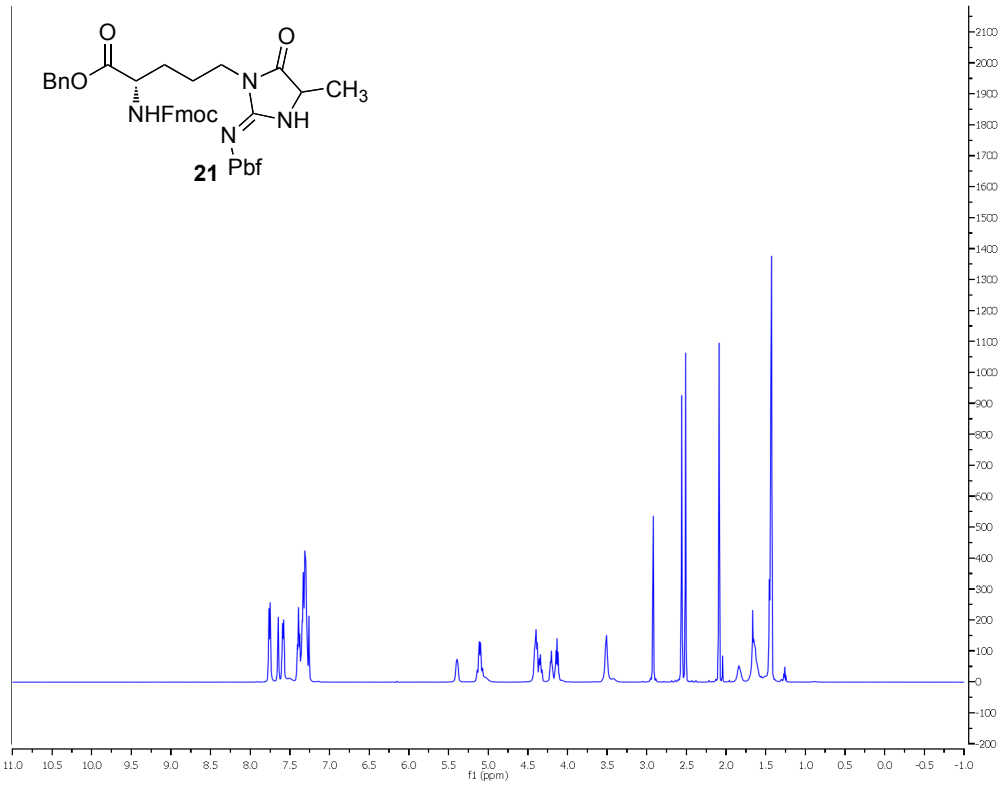
18_{free}•TFA

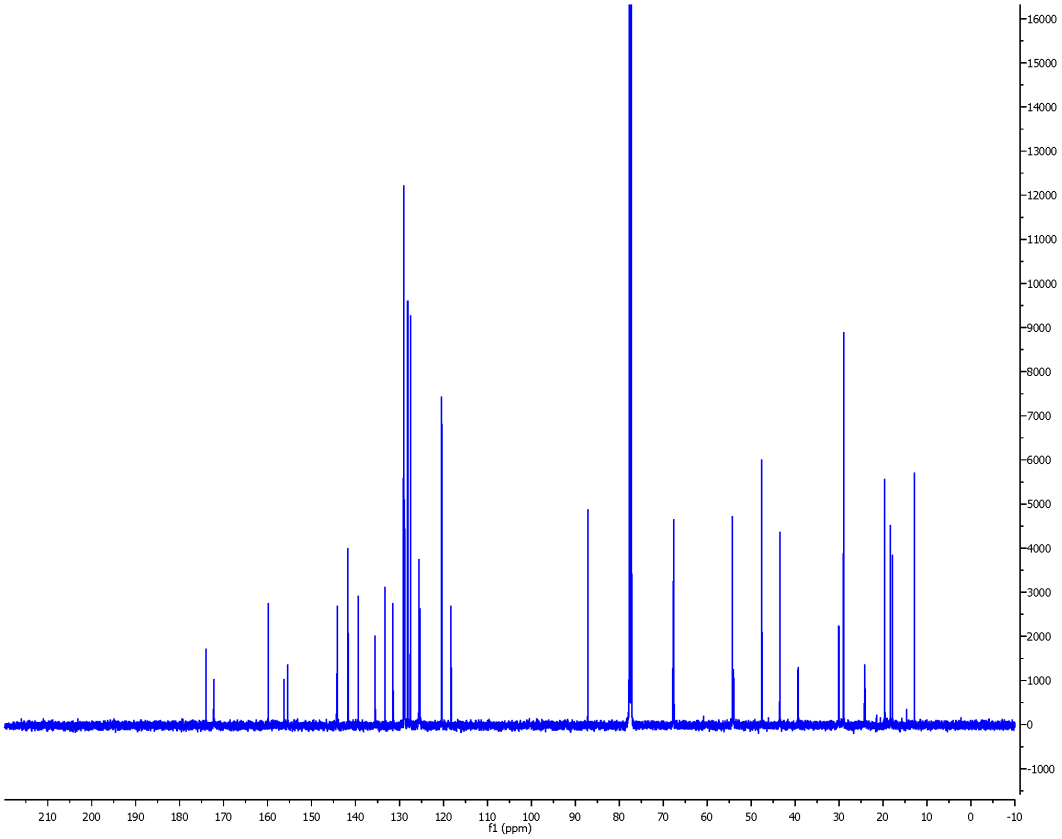


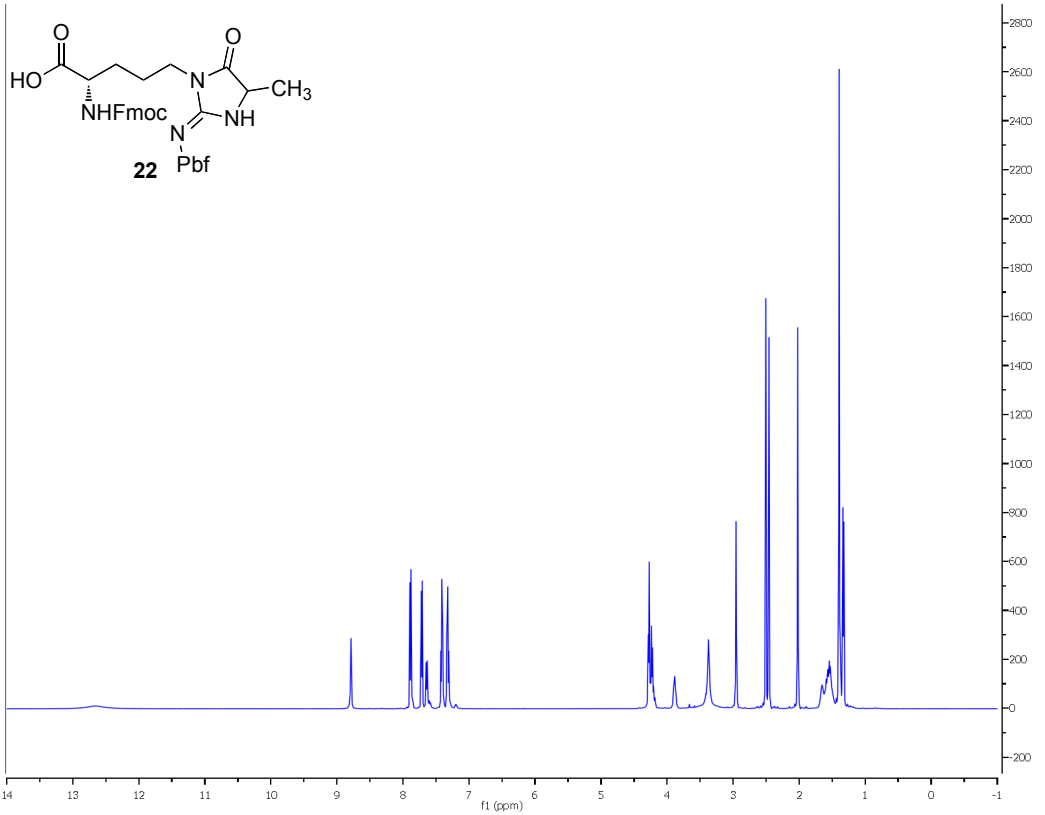


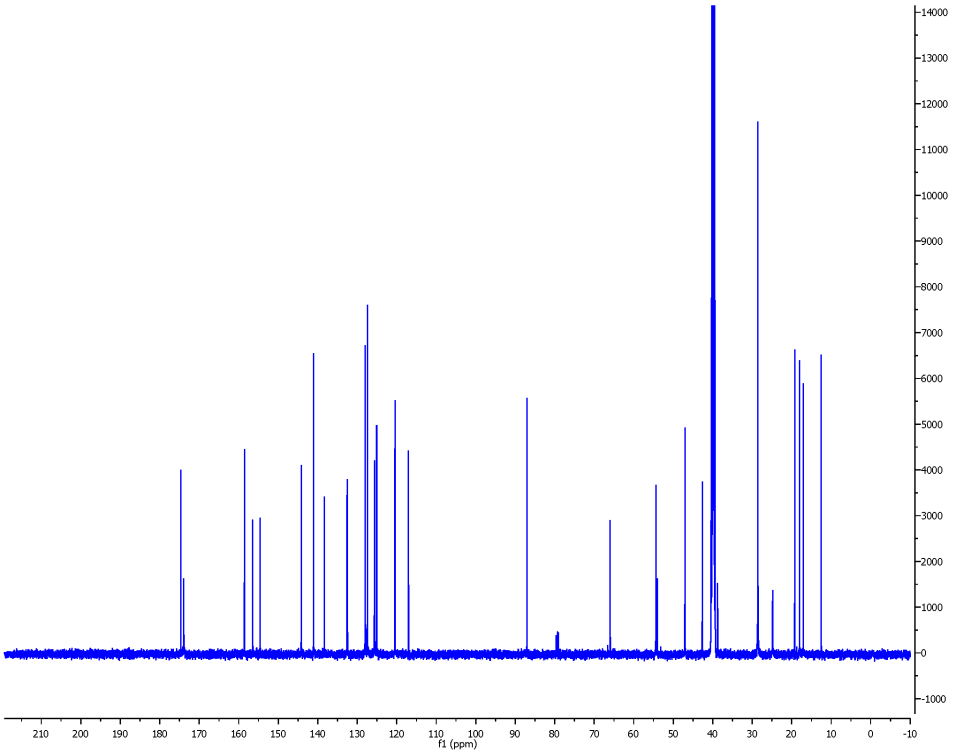
19

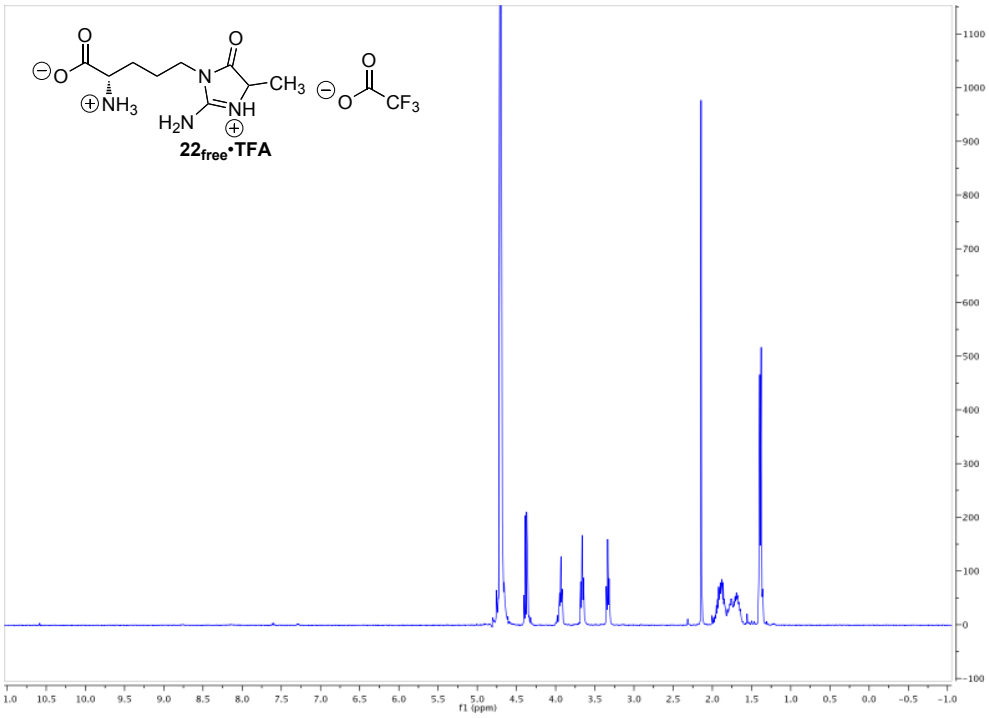

f1 (ppm)

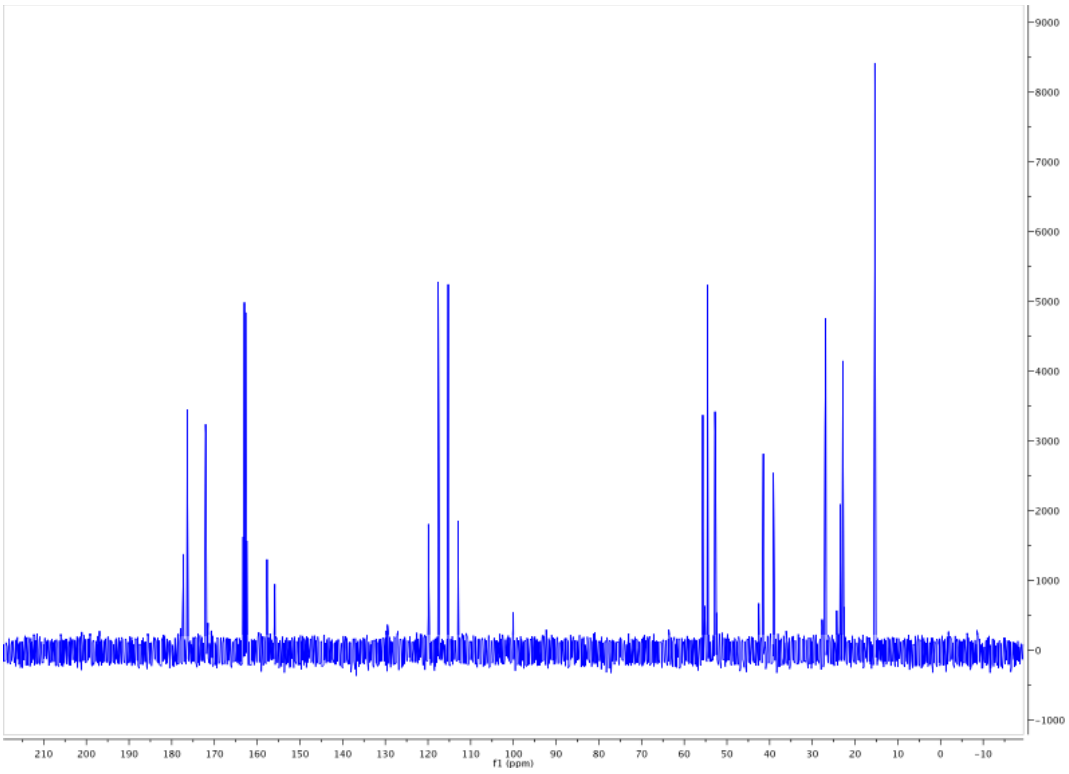

BnO
O
O
N
CH3
NHFmoc
NH
N
Pbf
21
f1 (ppm)


f1 (ppm)


HO
O
O
N
CH3
NHFmoc
NH
N
Pbf
22
f1 (ppm)


f1 (ppm)


22free•TFA
f1 (ppm)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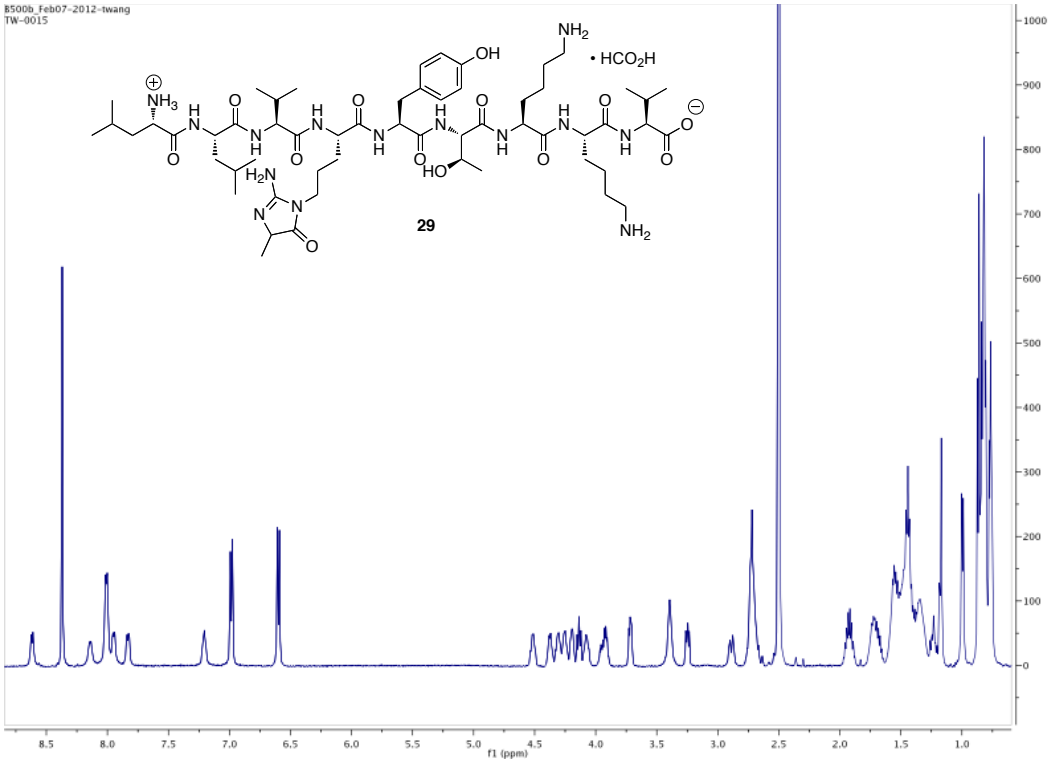
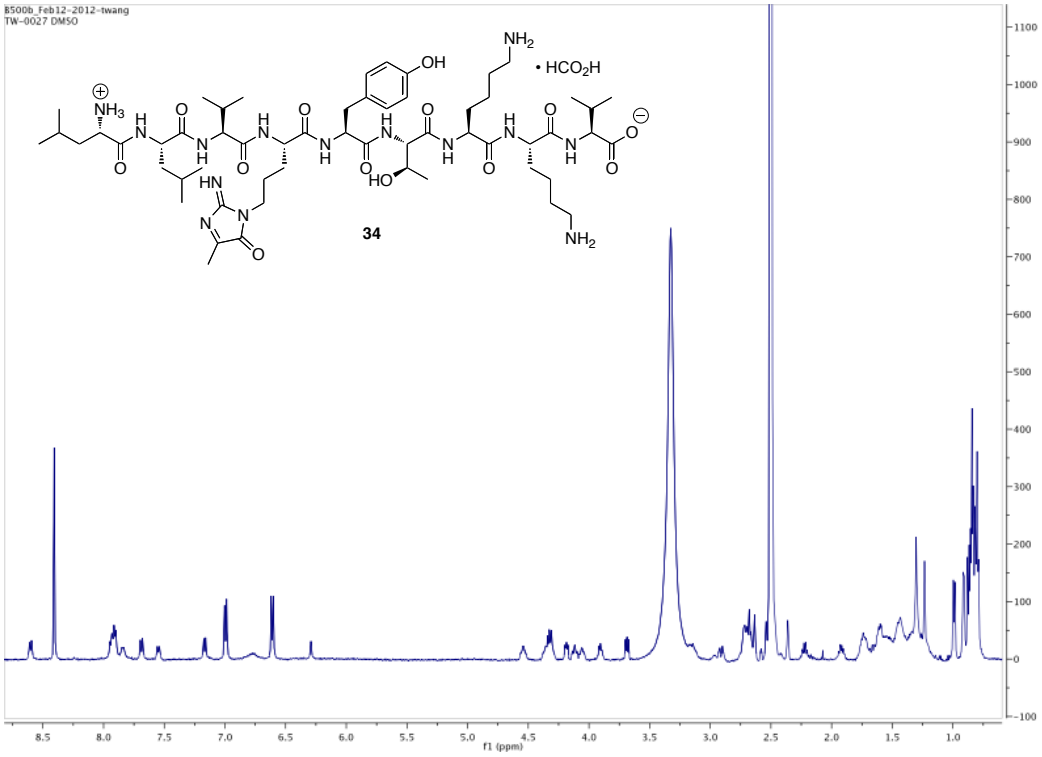

B500b_Feb07-2012-twang
TW-0015
29
f1 (ppm)


B500b_Feb12-2012-twang
TW-0027 DMSO
34
f1 (ppm)

CATALOG OF CALCULATED ABSOLUTE ENERGIES.

compound	SPE[a] (hartrees)	thermal correction[b] (hartrees)	free energy correction[c] (hartrees)
36a	-435.6231902	0.158126	0.114214
36a (gas phase)	-435.6007815	0.158367	0.115093
36a radical	-435.37764	0.145064	0.099613
[36a radical]$^+$	-435.37764	0.156758	0.112116
36b	-435.6136869	0.157905	0.114521
36c	-435.6149421	0.157650	0.114734
36d	-435.59342	0.157425	0.113033
37a	-435.624713	0.157842	0.114246
37a (gas phase)	-435.6008504	0.157826	0.114324
37a radical	-434.9892533	0.145166	0.101800
[37a radical]$^+$	-435.3834143	0.156495	0.113067
37b	-435.6181307	0.157793	0.114921
37c	-435.5985094	0.157618	0.113525
38a	-435.6203216	0.157886	0.115152
38a (gas phase)	-435.6055991	0.158094	0.115164
38a radical	-434.9975795	0.144841	0.099809
[38a radical]$^+$	-435.3954874	0.157741	0.113846
38b	-435.6205145	0.157941	0.115315
38c	-435.5925416	0.157293	0.112813
39a	-436.0782899	0.171638	0.128259
39a (gas phase)	-435.9894398	0.171295	0.127556
39a radical	-435.4426334	0.158670	0.114534
[39a radical]$^+$	-435.7780255	0.169271	0.125926
39b	-436.0307303	0.171638	0.129856
39c	-436.0087044	0.157293	0.127636
39d	-436.034716	0.171062	0.128459
40a	-436.0733098	0.171824	0.127871
40a (gas phase)	-435.9838682	0.171594	0.127250
40b	-436.035222	0.173321	0.129627
40c	-436.0266646	0.172869	0.128955
40d	-436.0536115	0.171830	0.127727
41a	-436.0751615	0.171544	0.127727
41a (gas phase)	-435.9849617	0.171213	0.126688
41b	-436.025515	0.173074	0.129572
41c	-436.0328556	0.172264	0.129992
41d	-436.0554917	0.171319	0.127352
42a	-436.0782896	0.171639	0.128262
42b	-436.0365627	0.173000	0.130123
42c	-436.0039276	0.171004	0.127838
42d	-436.0305668	0.170779	0.127550
43	-434.3898065	0.133840	0.089638
44	-434.3973653	0.133748	0.091544
45	-434.3902933	0.133463	0.091078

[a]Single point energy, calculated on B3LYP/6-31+(d) geometries. [b,c]Thermal corrections to SPE, obtained from frequency calculations on B3LYP/6-31+(d) geometries.

CATALOG OF CARTESIAN COORDINATES FROM B3LYP/6-31+(d) GEOMETRIES.

36a

C	-0.81427600	-0.25856500	-0.15576600
C	1.44481700	-0.51835400	-0.40990400
H	1.96062900	-0.55015800	-1.37719200
C	0.99862300	0.93356500	-0.12386300
O	1.78149800	1.88530500	-0.04408100
C	2.34930700	-1.09668000	0.68169500
H	2.62415300	-2.13144000	0.44981300
H	3.26795800	-0.50442100	0.74463800
H	1.85014700	-1.07563800	1.65677800
N	-0.36278200	0.99249600	0.02238400
N	0.13868700	-1.17019000	-0.51007500
H	0.01947800	-2.16272400	-0.34652500
N	-2.10047500	-0.59574200	-0.02217800
H	-2.36885600	-1.54800200	-0.23290400
C	-3.15333100	0.36012000	0.31227500
H	-3.29786300	1.08859700	-0.49241900
H	-4.07859000	-0.19874900	0.45879300
H	-2.90788600	0.89363900	1.23413200

36a gas phase

C	-0.81018200	-0.24464700	-0.13841300
C	1.44198400	-0.51775900	-0.42122400
H	1.94994900	-0.54037500	-1.39240100
C	1.00223700	0.94189100	-0.12007000
O	1.77879100	1.87662500	-0.04320400
C	2.35746900	-1.08808900	0.66250000
H	2.66323100	-2.11522200	0.42819900
H	3.25735700	-0.46879700	0.73287300
H	1.86074000	-1.08187800	1.64010100
N	-0.37888600	0.98705700	0.03596400
N	0.13546600	-1.18375200	-0.51917800
H	0.04328900	-2.13075700	-0.16772400
N	-2.09918400	-0.61709700	0.02559000
H	-2.37273800	-1.50137900	-0.38221500
C	-3.15378300	0.35945100	0.28505500
H	-3.42647800	0.91726200	-0.61941500
H	-4.03053800	-0.16980600	0.66705100
H	-2.80325900	1.06941700	1.03543600

36a radical

C	-0.84224500	-0.25859900	-0.00005500
C	1.37771100	-0.46621200	0.00002100

C	0.97360800	0.93454500	-0.00001200
O	1.74098800	1.92367700	0.00001100
C	2.72921600	-1.07494300	0.00004100
H	2.88910400	-1.70637700	-0.88468100
H	3.48379800	-0.28412800	0.00007900
H	2.88905900	-1.70642200	0.88473900
N	-0.42312300	0.99702100	-0.00005200
N	0.20512200	-1.17329600	0.00000700
H	0.11818300	-2.18233100	-0.00006600
N	-2.12314100	-0.66081700	-0.00020500
H	-2.32338200	-1.65186900	0.00044700
C	-3.23926500	0.27725200	0.00011600
H	-3.21258700	0.91510100	-0.88944800
H	-4.16481800	-0.29976600	-0.00076900
H	-3.21341500	0.91376000	0.89068900

36a radical cation

C	0.84709000	-0.29043900	0.07608400
C	-1.41876300	-0.52790900	0.37749500
H	-1.57613900	-0.33372400	1.44987300
C	-0.87686100	1.05509800	0.03481700
O	-1.70520900	1.92016900	-0.09684000
C	-2.63912200	-1.05641600	-0.32132500
H	-2.86847500	-2.06082600	0.05651300
H	-3.49549900	-0.41400000	-0.10486500
H	-2.48725900	-1.11574500	-1.40267200
N	0.45447700	1.00477900	0.08786100
N	-0.19324900	-1.18714500	0.13754400
H	-0.13898000	-2.11899800	-0.26636000
N	2.10526400	-0.66136900	-0.01378800
H	2.32163600	-1.64917700	0.07415200
C	3.22441600	0.27505100	-0.15535400
H	3.59271500	0.57837900	0.82902300
H	4.01831100	-0.22873300	-0.70701600
H	2.88936100	1.15531300	-0.70555300

36b

C	-0.79644900	-0.41073900	-0.07356900
C	1.39039400	-0.55517800	-0.43610700
H	1.78761500	-0.58357500	-1.46131300
C	1.04697800	0.90461700	-0.11153500
O	1.78671100	1.87920500	-0.03697900
C	2.44956200	-1.12572300	0.51546000
H	2.66608100	-2.16399000	0.24510100
H	3.37616300	-0.54584100	0.44766600
H	2.09417100	-1.10402700	1.55165800

N	0.11502500	-1.28046300	-0.38246100
N	-2.11335800	-0.67766500	0.13161100
H	-2.38056800	-1.61367900	-0.14790100
C	-3.16417900	0.33817700	0.11514000
H	-3.22036100	0.87435200	-0.84127400
H	-4.11682500	-0.16457600	0.28923800
H	-3.02007600	1.05981800	0.92565600
N	-0.31378500	0.89869100	0.09148300
H	-0.85290000	1.71701200	0.34624200

36c

C	1.09143700	0.72911900	0.42516700
H	1.31336300	0.86714500	1.49318800
N	0.08320300	-1.28483800	-0.14199400
H	-0.08467100	-2.25402800	-0.38483500
N	-0.34765200	0.87844400	0.17418800
H	-0.86031400	1.60111200	0.66355100
C	-0.95818400	-0.34675800	-0.02885000
C	1.96232400	1.67130600	-0.40646700
H	1.75066000	2.71139200	-0.13852900
H	3.02054900	1.47236900	-0.20927200
H	1.76813100	1.53843600	-1.47590400
C	1.31743200	-0.75160900	0.09580100
O	2.39116400	-1.34117800	0.05357500
N	-2.18930200	-0.67007900	-0.14336400
C	-3.16774000	0.40711800	-0.02317400
H	-4.16175600	0.01215900	-0.25013800
H	-3.20399200	0.82429100	0.99553600
H	-2.96664800	1.23680200	-0.71886700

36d

C	0.88341400	-0.30097400	-0.04856700
C	-1.34895400	-0.50163900	0.00169000
C	-0.94800900	0.80838000	-0.01631500
C	-2.67605000	-1.18391000	0.05408100
H	-2.79483700	-1.78936100	0.96330400
H	-3.48827100	-0.44910300	0.04746900
H	-2.83446900	-1.84746000	-0.80701000
N	0.42167300	0.94370500	-0.04298000
N	-0.13018100	-1.20983400	-0.01567900
H	-0.03653600	-2.21632400	-0.05482400
N	2.21300000	-0.66533000	-0.15014000
H	2.42291200	-1.56124500	0.27623500
C	3.22869400	0.35559600	0.10215400
H	3.16339000	0.78247100	1.11351300
H	4.21158500	-0.10232400	-0.03070600

H	3.12028600	1.16695200	-0.62189000
O	-1.68705100	1.96506100	-0.00026900
H	-2.63366500	1.75140500	0.01940200

37a

C	-0.94830300	-0.73350700	0.10436700
C	1.20196600	-0.77522800	-0.16193700
N	-0.67050800	0.58078600	-0.05511200
N	-2.20031300	-1.19615600	0.24611200
H	-2.99148500	-0.58106100	0.37178900
H	-2.32839000	-2.17339100	0.47075700
N	0.11329100	-1.56074800	0.09147400
C	-1.64215200	1.62515400	-0.34926100
H	-2.44283400	1.63036100	0.39663700
H	-1.14031300	2.59269800	-0.29772600
H	-2.07724700	1.50523700	-1.34989100
C	1.50170900	1.65625000	0.60995500
H	1.35529000	1.36850000	1.65655700
H	2.57240700	1.62971300	0.38432400
H	1.15224500	2.68543500	0.47696500
C	0.76647300	0.69715400	-0.32558600
H	0.92160800	0.99841600	-1.37155700
O	2.37540800	-1.15525200	-0.24755000

37a gas phase

C	-0.95753900	-0.72282900	0.10708900
C	1.18788000	-0.80473600	-0.16111000
N	-0.65764300	0.60471700	-0.02190300
N	-2.23241300	-1.14696900	0.31286600
H	-3.01818500	-0.57105600	0.05046700
H	-2.36849500	-2.14782600	0.26498900
N	0.05813000	-1.56816800	0.08040800
C	-1.60078700	1.65880700	-0.33987900
H	-2.47996300	1.59819700	0.31073800
H	-1.12869300	2.62587100	-0.14874600
H	-1.92628900	1.63473200	-1.39206800
C	1.56124400	1.62569100	0.58584300
H	1.40050900	1.36921000	1.63848300
H	2.62785100	1.52051000	0.36384300
H	1.27790500	2.67395300	0.43230000
C	0.77556400	0.68540000	-0.32411400
H	0.91923700	0.97095100	-1.37774000
O	2.34018000	-1.19445000	-0.24360500

37a radical

C	1.03603000	-0.69752900	0.00264300
C	-1.11861800	-0.89086000	-0.00079100
N	0.56217600	0.61065100	-0.00223300
N	2.36482300	-0.95943100	-0.05280900
H	3.03015900	-0.26317200	0.25814700
H	2.63734800	-1.91885000	0.12199900
N	0.07970100	-1.60741300	-0.00001600
C	1.38813800	1.81425700	-0.00765200
H	2.10321000	1.77629000	-0.83451900
H	0.74511400	2.68317400	-0.14447100
H	1.92481300	1.92111000	0.94067100
C	-1.73350800	1.68998000	0.00665800
H	-1.61458900	2.31725300	-0.88752700
H	-2.76127700	1.31860100	0.02689800
H	-1.58334300	2.33476200	0.88303600
C	-0.80753400	0.53246400	0.00208000
O	-2.26442400	-1.39571200	0.00044400

37a radical cation

C	-0.97712300	-0.74239200	0.07658500
C	1.21739900	-0.76158200	-0.15825300
N	-0.65007800	0.55942700	-0.18125500
N	-2.20693600	-1.17865400	0.28596700
H	-3.01729700	-0.57264200	0.30876100
H	-2.35289900	-2.16668300	0.45785800
N	0.10043500	-1.56533700	0.08026200
C	-1.60271700	1.64753600	-0.30392100
H	-2.05830200	1.85260600	0.67358000
H	-1.08608700	2.53704600	-0.65923900
H	-2.38806800	1.36899800	-1.01567100
C	1.46372800	1.67460900	0.62519300
H	1.26039000	1.39915200	1.66367500
H	2.54264400	1.64599900	0.45052700
H	1.11623000	2.69471000	0.44424700
C	0.80173400	0.69456700	-0.35150600
H	1.00056700	1.00130100	-1.38745400
O	2.35759300	-1.19312200	-0.19496000

37b

C	1.05308700	-0.78821700	-0.13000900
C	-1.23766500	-0.68147900	0.16418300
N	0.74054400	0.54752300	-0.01370200
N	2.17289100	-1.40607700	-0.26238400
H	2.95896300	-0.75669000	-0.26212500
C	1.73866500	1.54350200	0.34373200
H	2.61683600	1.44481900	-0.30002000

H	1.32122100	2.53883100	0.18057500
H	2.04999700	1.45503100	1.39428300
C	-1.39958700	1.75341000	-0.57068300
H	-1.31295600	1.47961600	-1.62725200
H	-2.45902900	1.79027000	-0.29848300
H	-0.97896100	2.75393000	-0.43113700
C	-0.67850600	0.73615600	0.31577000
H	-0.78712400	1.02553500	1.37309100
O	-2.40986500	-1.02639500	0.25379100
N	-0.16604900	-1.48584800	-0.09211000
H	-0.21770000	-2.48960500	-0.21985500

37c

C	1.02791000	-0.72928900	0.00392000
C	-1.10857900	-0.70673100	-0.00370900
N	0.65963000	0.57840700	-0.01361200
N	2.35911300	-1.13687900	-0.07162900
H	2.97835700	-0.67927200	0.59258500
H	2.43402200	-2.14422900	0.03390300
N	-0.02143300	-1.54535200	0.00360700
C	1.55337100	1.72682800	-0.02300600
H	2.47119200	1.46526500	-0.55542600
H	1.07357900	2.55574800	-0.54703200
H	1.80582700	2.04888600	0.99393700
C	-1.55297800	1.87434800	0.02145800
H	-1.39872600	2.49129800	-0.87490400
H	-2.61707400	1.62254700	0.06507500
H	-1.32551200	2.50183400	0.89418800
C	-0.75312800	0.61495400	0.00051100
O	-2.38529400	-1.20514500	-0.00619900
H	-2.32006600	-2.17481000	0.02365400

38a

C	1.30266800	-0.50145000	-0.41427400
C	-0.85690000	-0.85403700	-0.08727800
H	1.72120900	-0.51067500	-1.43081100
N	0.23539400	-1.50489000	-0.31903700
C	2.43839500	-0.73618700	0.58884500
H	2.90286100	-1.70899400	0.39924800
H	3.20202000	0.04232600	0.48912400
H	2.05760300	-0.72772200	1.61616300
C	0.61184100	0.84841500	-0.20481300
O	1.10173800	1.97411800	-0.19860400
N	-0.71831500	0.54460300	-0.00769600
C	-1.76502600	1.51758400	0.26936300
H	-1.28575200	2.49353200	0.36422900

H	-2.49149500	1.55843500	-0.54893500
H	-2.27685100	1.27529100	1.20526500
N	-2.08418100	-1.41086600	0.15305200
H	-2.90563700	-0.87357900	-0.09800300
H	-2.15400900	-2.38943500	-0.10275100

38a gas phase

C	1.29915500	-0.50856300	-0.41443900
C	-0.85688200	-0.84824900	-0.09141500
H	1.72046200	-0.53103200	-1.42964700
N	0.22551000	-1.50442200	-0.31897500
C	2.42812100	-0.74737600	0.59435700
H	2.88639000	-1.72378600	0.40935900
H	3.19022100	0.03322500	0.50093000
H	2.03966600	-0.73942900	1.61878100
C	0.62101100	0.85305200	-0.21369800
O	1.10569900	1.97153000	-0.20026000
N	-0.72365600	0.54943000	-0.02386500
C	-1.74839800	1.52920000	0.28424000
H	-1.24757800	2.49547400	0.38277200
H	-2.49046700	1.60209400	-0.52070100
H	-2.25275300	1.28331800	1.22488800
N	-2.09193600	-1.40950000	0.15780300
H	-2.90155600	-0.90839600	-0.18818900
H	-2.11744300	-2.40065000	-0.05511800

38a radical

C	-1.25583600	-0.44598000	-0.00222500
C	0.85988600	-0.85757400	0.00320400
N	-0.34717700	-1.45113900	-0.00092800
C	-2.72835000	-0.66711100	0.00183900
H	-3.04843500	-1.18825400	0.91422900
H	-3.26034900	0.28692800	-0.05268800
H	-3.03642100	-1.28742400	-0.84975400
C	-0.59094900	0.84269800	0.00125000
O	-1.03261600	2.00618000	0.00208600
N	0.78695100	0.50532800	0.00364700
C	1.88348700	1.45998800	-0.00360200
H	1.44403300	2.45674300	-0.07169300
H	2.47065800	1.39409700	0.91846500
H	2.53464700	1.29704200	-0.86800800
N	2.02673900	-1.53729900	-0.04880500
H	2.89739100	-1.08379600	0.19535900
H	1.98438400	-2.53513300	0.11720600

38a radical cation

C	1.32417500	-0.44203800	-0.40266400
C	-0.88031800	-0.83088900	-0.05724800
H	1.68735900	-0.47615700	-1.44325400
N	0.31966300	-1.47530500	-0.27062200
C	2.52474500	-0.66660700	0.53703500
H	2.99148300	-1.62681300	0.30593500
H	3.25138800	0.13366300	0.37553600
H	2.20637100	-0.66080500	1.58299000
C	0.58517100	0.87653900	-0.18344300
O	1.00007400	2.00861500	-0.16286100
N	-0.77509300	0.51458100	0.00808000
C	-1.85878700	1.46976200	0.23183700
H	-1.41286300	2.46419900	0.24499500
H	-2.58687700	1.40436300	-0.58115400
H	-2.33921700	1.27011000	1.19345000
N	-1.99061700	-1.52309000	0.06838100
H	-2.89755800	-1.09510000	0.22513000
H	-1.94826300	-2.53629200	0.00528800

38b

C	-0.89726500	-0.94194100	-0.07810800
N	-0.80039200	0.46590200	-0.01072900
N	-1.92314900	-1.68281700	0.14016800
H	-2.73965400	-1.13028700	0.39861200
C	-1.92836600	1.34605800	0.25261600
H	-2.33094400	1.17117300	1.25550400
H	-1.56827200	2.37327300	0.18592600
H	-2.71514200	1.18979600	-0.49143200
N	0.34220700	-1.40316600	-0.45726200
H	0.58287100	-2.35939100	-0.22871700
C	1.35230400	-0.34831200	-0.42252200
H	1.84838000	-0.25670200	-1.39688100
C	2.40996600	-0.52194200	0.67479700
H	2.99153800	-1.43176500	0.49307000
H	3.09632600	0.33074200	0.66744300
H	1.94328200	-0.59432100	1.66303500
C	0.49073600	0.89529700	-0.20530700
O	0.87458900	2.05913600	-0.19758200

38c

C	-0.63464800	0.70077300	0.00191200
C	-1.20842600	-0.54000800	-0.00471000
C	0.94039000	-0.83871500	0.01341600
N	0.75483800	0.51273100	-0.00287200
N	2.21165600	-1.40676700	-0.06833300

H	2.89539800	-1.00052800	0.56542600
H	2.16779700	-2.41157700	0.07482500
N	-0.20104300	-1.50534800	0.01229400
C	1.77846100	1.54557900	-0.04079000
H	1.30220000	2.49166200	-0.30273800
H	2.27127300	1.65428900	0.93180200
H	2.52717500	1.29849700	-0.79904400
C	-2.65922400	-0.90328900	-0.01253300
H	-3.28323300	-0.00434400	-0.04655500
H	-2.91086100	-1.52331500	-0.88293700
H	-2.93679400	-1.47366100	0.88384700
O	-1.17146600	1.95719500	-0.07182000
H	-1.31869800	2.32106100	0.81855300

39a

C	1.35119200	-0.44050200	-0.40908600
C	-0.90708900	-0.81500300	-0.05933200
H	1.74048200	-0.45864300	-1.43394100
C	2.48530500	-0.65088100	0.59675700
H	2.97552000	-1.61059000	0.40900300
H	3.22473000	0.14605200	0.47605900
H	2.10711500	-0.63746900	1.62335500
C	0.59941500	0.87327400	-0.20234000
O	1.05124500	1.99844500	-0.19837400
N	-0.74791900	0.54457200	-0.00098100
C	-1.80638100	1.52372600	0.24509900
H	-1.33424600	2.50612100	0.23404100
H	-2.55893000	1.47851500	-0.54630300
H	-2.26370100	1.35579800	1.22359700
N	-2.07465400	-1.41611900	0.09129000
H	-2.92473000	-0.89259800	0.25648700
H	-2.15421900	-2.42516900	0.05176900
N	0.26093400	-1.41171700	-0.28047700
H	0.37483600	-2.41041000	-0.40249600

39a gas phase

C	1.36178300	-0.43686000	-0.41049700
C	-0.90829500	-0.81133300	-0.05924700
H	1.74679000	-0.45168300	-1.43787200
C	2.49909200	-0.64627200	0.59161500
H	3.01535600	-1.59074300	0.39363800
H	3.22087200	0.16849100	0.48242100
H	2.12691000	-0.65093000	1.62069800
C	0.60866100	0.87902900	-0.20099100
O	1.04024500	1.99852500	-0.18960800

N	-0.76128600	0.53659400	-0.00271600
C	-1.81539800	1.52452000	0.23943000
H	-1.33470400	2.50414500	0.21715700
H	-2.57187500	1.48229200	-0.54986500
H	-2.26872700	1.37374400	1.22380500
N	-2.07658500	-1.42832300	0.09680500
H	-2.92745900	-0.90768100	0.26803700
H	-2.15570500	-2.43675200	0.04731000
N	0.26192500	-1.41120300	-0.28634800
H	0.38314000	-2.41306100	-0.36450500

39a radical

C	-1.29744200	-0.37527700	-0.00003300
C	0.90730200	-0.82958400	0.00003400
C	-2.75736400	-0.60907000	0.00002500
H	-3.06563800	-1.17872900	0.88599100
H	-3.27938000	0.35011600	-0.00031400
H	-3.06560000	-1.17941100	-0.88550600
C	-0.58075500	0.87638700	-0.00000800
O	-0.99542000	2.03431400	-0.00003100
N	0.80372100	0.51289000	0.00007600
C	1.90501800	1.47319500	-0.00001100
H	1.45536100	2.46631900	0.00005600
H	2.51585900	1.35446000	0.89851300
H	2.51568800	1.35449100	-0.89865700
N	2.03080900	-1.52954200	-0.00002200
H	2.93512800	-1.07387700	0.00010800
H	2.02328500	-2.54259400	-0.00005200
N	-0.34726800	-1.36590500	-0.00003500
H	-0.54273600	-2.36129300	-0.00006100

39a radical cation

C	1.35270400	-0.37450800	-0.37375300
C	-0.92062700	-0.83223600	-0.02208100
H	1.57928700	-0.36108300	-1.46209800
C	2.65302500	-0.58232800	0.40767700
H	3.12207600	-1.52346500	0.11080000
H	3.32912300	0.23718600	0.15573800
H	2.45538600	-0.58815400	1.48231400
C	0.54517200	0.91016000	-0.12449600
O	0.94496700	2.04049700	-0.08732700
N	-0.80945400	0.52066700	0.02676200
C	-1.92124400	1.46397900	0.15075500
H	-1.49281900	2.46243400	0.21935700
H	-2.56901400	1.39072600	-0.72790000
H	-2.48121700	1.23402900	1.06324600

N	-2.01338300	-1.53577200	0.05924600
H	-2.92553100	-1.09988700	0.17532500
H	-2.00408800	-2.55117200	-0.01187000
N	0.34159100	-1.36637500	-0.15674000
H	0.54162000	-2.36463400	-0.03979100

39b

C	1.30910900	-0.55833100	-0.41231600
C	-0.83714500	-0.73874900	-0.08895100
H	1.69620200	-0.61716300	-1.43751100
N	0.16431500	-1.48582700	-0.30751100
C	2.42682800	-0.89594900	0.57959900
H	2.81519900	-1.89632500	0.37022400
H	3.23946100	-0.17122800	0.47416400
H	2.05764100	-0.86703500	1.60951000
C	0.71487700	0.83923100	-0.19928900
O	1.26764200	1.92272900	-0.18715800
N	-0.65700700	0.62626400	-0.00562700
C	-1.63676100	1.67707800	0.26514300
H	-1.08152300	2.61474400	0.31405300
H	-2.37289800	1.74164100	-0.54033700
H	-2.13354400	1.50820800	1.22413100
N	-2.17723500	-1.31200600	0.06956800
H	-2.82848400	-1.01948700	-0.67303200
H	-2.09342700	-2.33739000	0.02300500
H	-2.61171600	-1.07648900	0.97293000

39c

C	1.25919700	-0.67284800	-0.36509100
C	-0.99730400	-0.78673200	-0.17577000
H	1.70448300	-0.85839500	-1.35330500
N	0.06307000	-1.49019000	-0.21240700
C	2.31996700	-0.94234900	0.71308000
H	2.63056100	-1.98790900	0.64012800
H	3.19269000	-0.30300400	0.55353800
H	1.91670800	-0.76233300	1.71379300
C	0.79040800	0.76930000	-0.36093800
O	1.33349500	1.82166800	-0.35108800
N	-0.78493900	0.68948600	-0.33158400
C	-1.38820800	1.59106000	0.71902300
H	-0.98112600	2.58900700	0.55598700
H	-2.46995600	1.59915300	0.59772600
H	-1.10924800	1.21115900	1.70072000
N	-2.26207100	-1.19205000	0.06871700
H	-3.05006200	-0.66535100	-0.28874200
H	-2.40191900	-2.19657400	0.09131900

H	-1.11687600	0.99960400	-1.25736600

39d

C	1.25447500	-0.59678500	-0.41158000
C	-0.92143200	-0.86644300	-0.09685800
H	1.67859100	-0.60567400	-1.42616100
N	0.14579000	-1.54239200	-0.33475000
C	2.37182600	-0.89774400	0.60386400
H	2.74745300	-1.90461400	0.40576500
H	3.20471900	-0.19500600	0.50076900
H	1.98796500	-0.85776500	1.62710000
C	0.59372800	0.74177100	-0.19350000
O	1.10594200	1.93692700	-0.17090800
N	-0.69237200	0.55877300	-0.00022900
C	-1.69987300	1.58999000	0.27490700
H	-1.19313400	2.54861700	0.37724400
H	-2.40835400	1.63863200	-0.55514800
H	-2.21550800	1.34481500	1.20520100
N	-2.17079900	-1.32839600	0.13709100
H	-2.96961000	-0.73499100	-0.04881700
H	-2.32017500	-2.30997100	-0.06657900
H	2.06983200	1.93991000	-0.32789600

40a

C	-0.84621400	-0.35062300	-0.10683100
C	1.45352600	-0.52995200	-0.40343400
H	1.84307400	-0.59087600	-1.42692700
C	1.04966300	0.92173200	-0.13190700
O	1.76241500	1.89765900	-0.05406300
C	2.48620700	-1.06524600	0.59067100
H	2.73014600	-2.10442900	0.35123800
H	3.40003300	-0.46884600	0.51438700
H	2.10830700	-1.01358900	1.61606300
N	0.15268000	-1.20622800	-0.33139100
H	0.02092300	-2.19266200	-0.51638000
N	-2.12961500	-0.64113100	-0.01837800
H	-2.39385100	-1.61428300	-0.12128700
C	-3.19326300	0.33771200	0.24447600
H	-3.18521800	1.12767000	-0.51141900
H	-4.14368900	-0.19065200	0.18574500
H	-3.08894500	0.76770900	1.24482700
N	-0.33836600	0.91487100	0.02223200
H	-0.88248900	1.74436100	0.23116000

40a gas phase

C	-0.84776600	-0.34350500	-0.11214800
C	1.46590900	-0.53039300	-0.40510400
H	1.86103600	-0.59033700	-1.42715900
C	1.06682800	0.92561100	-0.13302600
O	1.76126600	1.89796000	-0.04761900
C	2.48911600	-1.06974400	0.59670000
H	2.75464800	-2.10334600	0.35404600
H	3.39588000	-0.46042900	0.53862800
H	2.10385900	-1.03016200	1.62018900
N	0.15177000	-1.20164900	-0.34775100
H	0.02310900	-2.19537700	-0.49062700
N	-2.13454400	-0.64461500	-0.01355000
H	-2.39921200	-1.61655800	-0.12395300
C	-3.20349700	0.33355800	0.24872300
H	-3.23902200	1.08957400	-0.54160300
H	-4.15149600	-0.20421300	0.25269200
H	-3.06852400	0.80462400	1.22725300
N	-0.34718900	0.91464800	0.01604800
H	-0.88421300	1.75069500	0.21738400

40b

C	-0.88120600	-0.19621600	-0.07865500
C	1.47447500	-0.47546100	-0.39730500
H	1.82500300	-0.54064500	-1.42976100
C	0.98217400	0.96119200	-0.12010900
O	1.73014100	1.91691500	-0.05501000
C	2.52604200	-0.98273700	0.58013600
H	2.83353200	-2.00235800	0.32985000
H	3.40053600	-0.33105400	0.50336900
H	2.16407200	-0.95232400	1.61344700
N	-0.39879100	1.00156000	0.03388000
N	-2.13427500	-0.58770400	-0.00645800
H	-2.36026600	-1.57176800	-0.10027300
C	-3.23413800	0.35336900	0.24367400
H	-3.22559700	1.14236100	-0.51150600
H	-4.16693600	-0.20552300	0.18414000
H	-3.12968800	0.79551600	1.23784300
N	0.16897800	-1.25692000	-0.31751100
H	-0.01842800	-1.79045700	-1.17609900
H	0.18118800	-1.93849400	0.45324500

40c

C	-0.74496600	-0.26327100	-0.15384500
C	1.48201900	-0.51903300	-0.38405900
H	1.89199600	-0.59553000	-1.39845500
C	1.02714400	0.93762800	-0.14191200

O	1.76293700	1.90406200	-0.06460900
C	2.48815800	-1.03928600	0.64317700
H	2.76568000	-2.07285500	0.41608200
H	3.38911500	-0.42023900	0.59946100
H	2.07446700	-0.99393100	1.65501700
N	-0.37595500	0.97642000	-0.01868300
N	-2.16653300	-0.63836900	-0.10252200
H	-2.46363100	-0.93994400	-1.04176900
C	-3.09727900	0.45356400	0.38346000
H	-3.00504800	1.30238900	-0.28884300
H	-4.10287100	0.03674300	0.36079700
H	-2.80305900	0.72232200	1.39560400
N	0.18067400	-1.20036200	-0.34058200
H	0.03161100	-2.18538500	-0.52573000
H	-2.27951200	-1.46750400	0.49629200

40d

C	-0.87037900	-0.31908000	-0.10697000
C	1.39232700	-0.57389800	-0.40231000
H	1.79870700	-0.62329200	-1.42157000
C	0.92044900	0.84048900	-0.11929300
O	1.70455400	1.89339100	-0.03721600
C	2.41187000	-1.13126400	0.59972300
H	2.61313600	-2.18048200	0.36576700
H	3.35847200	-0.58671200	0.52318100
H	2.03552700	-1.05816700	1.62382100
N	-0.36269500	0.95834900	0.04867600
N	-2.16120100	-0.57812000	-0.02200900
H	-2.45701800	-1.54054100	-0.14582800
C	-3.20720700	0.41026400	0.25570600
H	-3.94901700	0.38312500	-0.54623600
H	-3.68967300	0.17519900	1.20825200
H	-2.75775700	1.40005800	0.30672600
N	0.08785100	-1.22836200	-0.34798100
H	-0.06111200	-2.21079500	-0.54258200
H	2.64226300	1.67234200	-0.18574200

41a

C	-0.97390300	-0.72012500	0.07091400
C	1.28856900	-0.67958400	-0.17194900
N	-0.69319300	0.55589200	-0.16908700
N	-2.17771400	-1.23024700	0.27539000
H	-3.00357000	-0.64523100	0.29392300
H	-2.31061800	-2.22175900	0.43065100
C	-1.68504600	1.62223600	-0.30742700
H	-2.12400700	1.87545700	0.66211900

H	-1.18425500	2.50220900	-0.71013100
H	-2.46857600	1.32355000	-1.00969600
C	1.38798500	1.73051300	0.64123400
H	1.19323700	1.43108700	1.67536600
H	2.46872700	1.75607500	0.47441300
H	0.99400400	2.73771500	0.48054800
C	0.76008500	0.74517000	-0.34771400
H	0.95350100	1.06420500	-1.37940600
O	2.43688800	-1.06479900	-0.21889900
N	0.17205000	-1.47199500	0.07480900
H	0.21231300	-2.46971600	0.25526800

41a gas phase

C	-0.97325200	-0.72092600	0.07050100
C	1.30132000	-0.67889500	-0.17656300
N	-0.69178600	0.55543200	-0.17317800
N	-2.19150500	-1.21801900	0.27858900
H	-3.00946700	-0.62254100	0.29842300
H	-2.33986600	-2.20605000	0.44137600
C	-1.68445500	1.62349400	-0.30954600
H	-2.11860500	1.88782500	0.66053000
H	-1.18634800	2.50353200	-0.71740800
H	-2.47187700	1.32886400	-1.01123900
C	1.39876100	1.72743500	0.64536100
H	1.19622600	1.43138300	1.67942800
H	2.48167400	1.73404300	0.48981200
H	1.02560500	2.74308000	0.48462300
C	0.76916000	0.74778600	-0.34860100
H	0.96164400	1.06993400	-1.38024300
O	2.43169500	-1.07544200	-0.21913000
N	0.15873800	-1.47809600	0.07506600
H	0.21012400	-2.47511300	0.25748400

41b

C	-0.90418500	-0.64436500	0.06389600
C	1.21231300	-0.82524700	-0.16706300
N	-0.60438500	0.63491800	-0.12677500
N	-2.28685200	-1.08606400	0.27250100
H	-2.71548900	-0.68008000	1.11640500
H	-2.27807000	-2.10853800	0.39354800
C	-1.47570300	1.79039300	-0.33801200
H	-2.47869400	1.59551500	0.04405500
H	-1.06666500	2.64357100	0.20584600
H	-1.53240400	2.02790300	-1.40492600
C	1.60719900	1.58044100	0.63937000

H	1.37519700	1.32198700	1.67710500
H	2.68152600	1.45420200	0.47605200
H	1.35643200	2.63054100	0.46553100
C	0.86128700	0.66762700	-0.33458800
H	1.05701800	0.96741800	-1.37209900
O	2.33398000	-1.29808600	-0.22767900
N	0.03747900	-1.54969800	0.07792700
H	-2.89984300	-0.87501500	-0.52727500

41c

C	-1.02581600	-0.69961000	0.20881200
C	1.10822700	-0.83076800	-0.26274500
N	-0.62287900	0.75750100	0.13599200
N	-2.28485600	-0.97269300	0.49179600
H	-2.98023400	-0.27279600	0.71924100
C	-1.42694500	1.57208100	-0.85859200
H	-2.45855400	1.64051800	-0.51716200
H	-0.98493500	2.56686700	-0.89662900
H	-1.37042500	1.08182600	-1.83005600
C	1.72892800	1.40010400	0.85568500
H	1.57396000	0.99248400	1.85959500
H	2.77721000	1.24978900	0.58322200
H	1.52878100	2.47524800	0.86187900
C	0.86999500	0.68733200	-0.18077800
H	1.00667800	1.12324200	-1.17299000
O	2.19123900	-1.32639300	-0.50121100
N	-0.06802000	-1.53540300	-0.02671800
H	-2.56964100	-1.94463400	0.55369700
H	-0.74879600	1.17794000	1.06710300

41d

C	-0.93541600	-0.78505000	0.07329900
C	1.17731300	-0.65001200	-0.14565800
N	-0.76112800	0.51040800	-0.19650000
N	-2.09876200	-1.37685400	0.29399300
H	-2.97541000	-0.87224100	0.31080400
C	-1.80378500	1.52463900	-0.33129900
H	-2.16703200	1.84961500	0.64861100
H	-1.38852200	2.38137300	-0.86307600
H	-2.63349400	1.12862700	-0.92316400
C	1.23039600	1.77954500	0.67227600
H	1.04421500	1.44922900	1.69796400
H	2.30726200	1.91021200	0.52796700
H	0.75767000	2.75326600	0.51844400
C	0.67773500	0.76783100	-0.34209300
H	0.88920900	1.10155400	-1.36672800

O	2.43803500	-1.02425000	-0.19612000
N	0.24024900	-1.51458000	0.10193500
H	-2.11942100	-2.37264300	0.47487400
H	3.04127300	-0.28952000	-0.41187500

42a

C	-0.90706900	-0.81499200	-0.05942200
N	-0.74782300	0.54460800	-0.00089500
N	-2.07458000	-1.41616500	0.09138400
H	-2.92461200	-0.89271400	0.25696600
C	-1.80627600	1.52377100	0.24517600
H	-2.26334000	1.35614500	1.22384200
H	-1.33420700	2.50619500	0.23368900
H	-2.55900200	1.47824900	-0.54604400
N	0.26089100	-1.41165000	-0.28113100
H	0.37510000	-2.41044900	-0.40207900
C	1.35122700	-0.44045400	-0.40914400
H	1.74098900	-0.45841200	-1.43381400
C	2.48493700	-0.65105700	0.59712700
H	2.97506300	-1.61083400	0.40951000
H	3.22453400	0.14576100	0.47674100
H	2.10636300	-0.63763600	1.62358600
C	0.59944600	0.87330800	-0.20239000
O	1.05127000	1.99848800	-0.19847500
H	-2.15406100	-2.42521200	0.05180600

42b

C	-1.00543400	-0.87901700	-0.01913300
N	-0.83662700	0.48568500	0.01555300
N	-1.98466500	-1.66051400	0.06574000
H	-2.88114900	-1.18676000	0.18536900
C	-1.95416700	1.40911900	0.21490500
H	-2.43473400	1.20791500	1.17535500
H	-1.54504000	2.41892500	0.21320700
H	-2.67505500	1.30308700	-0.59978100
N	0.36714700	-1.46909100	-0.18210100
H	0.59456300	-2.00969300	0.66294100
C	1.35140600	-0.33063300	-0.40318200
H	1.64464700	-0.35833900	-1.45567100
C	2.56781000	-0.41144400	0.50945800
H	3.15709800	-1.30444400	0.28341400
H	3.19167500	0.46739300	0.32713200
H	2.27993200	-0.42041600	1.56563000
C	0.47491500	0.90073400	-0.17707700
O	0.86012600	2.05015200	-0.18066900
H	0.35889200	-2.14400300	-0.95641300

42c

C	-1.09818400	-0.86623800	-0.12305900
N	-0.86301900	0.62475900	-0.31662600
N	-2.22176000	-1.43341200	-0.00845000
H	-3.02462800	-0.80959100	-0.05328700
C	-1.52095500	1.52166700	0.70530900
H	-1.18686000	1.21937600	1.69661100
H	-1.21821200	2.54404400	0.48227600
H	-2.60021200	1.41731900	0.60842400
N	0.13110400	-1.43033500	-0.09288100
H	0.20931900	-2.44026500	-0.07588000
C	1.28556500	-0.58296000	-0.35622400
H	1.67977200	-0.76071500	-1.36863300
C	2.42105200	-0.72717300	0.66475600
H	2.81720800	-1.74509200	0.61543400
H	3.22745100	-0.03095000	0.41875100
H	2.06511500	-0.53067000	1.67958100
C	0.68031800	0.79953200	-0.36042600
O	1.16485600	1.88160400	-0.37650300
H	-1.21885200	0.88765000	-1.24769400

42d

C	-0.97614500	-0.95361900	-0.07045000
N	-0.77800900	0.49104400	-0.00131100
N	-2.05504300	-1.59487200	0.12065500
H	-2.84856100	-1.00080700	0.35277800
C	-1.86382500	1.44303000	0.25147200
H	-2.26085500	1.27824400	1.25548500
H	-1.46579100	2.45333600	0.17462100
H	-2.64514700	1.29621200	-0.49684900
N	0.24674500	-1.45893400	-0.40245800
H	0.43672500	-2.44794000	-0.30736700
C	1.30607800	-0.46264500	-0.41404800
H	1.77426800	-0.39739800	-1.40623100
C	2.39207300	-0.67338100	0.65615200
H	2.89093900	-1.62739800	0.46348000
H	3.14938200	0.11440700	0.60125800
H	1.95716800	-0.69245900	1.65891200
C	0.48385500	0.77911900	-0.19113100
O	0.90053300	2.00922500	-0.17105800
H	1.85955300	2.09431300	-0.33778600

43

C	0.81454100	-0.22743300	-0.00081700
C	-1.30146700	-0.57158300	0.00172000

C	-0.96255900	0.94108800	-0.00028500
O	-1.78729000	1.84856300	-0.00062600
C	-2.67490400	-1.12736800	0.00094200
H	-2.65931200	-2.21945700	0.00341100
H	-3.22547200	-0.76525700	0.87812000
H	-3.22226800	-0.76964700	-0.88008800
N	0.40943000	1.03931100	-0.00028400
N	-0.20537900	-1.24678500	0.00119400
N	2.06398900	-0.64821200	-0.00834800
H	2.19402000	-1.65465200	0.01103900
C	3.24423800	0.20951400	0.00359800
H	3.67369100	0.24834300	1.01021800
H	3.98508600	-0.19666200	-0.68857000
H	2.95720000	1.21332600	-0.30801000

44

C	0.91768700	-0.75412800	-0.00269000
C	-1.24880700	-0.73120200	-0.00668000
N	0.63572300	0.58623300	-0.03318100
N	2.16879400	-1.22679100	0.00271700
H	2.97733800	-0.63666700	0.13617100
H	2.30210700	-2.22627900	0.07932500
N	-0.15387300	-1.55814000	-0.00230700
C	1.57513400	1.69790600	-0.01135900
H	2.52138600	1.40079800	-0.46775200
H	1.16673000	2.51758700	-0.60709600
H	1.75515700	2.04881200	1.01081300
C	-1.50497800	1.81581800	0.03053600
H	-2.58550100	1.72249900	0.04327800
H	-1.07977200	2.81384400	0.04852500
C	-0.76261100	0.70315900	-0.00352900
O	-2.43381200	-1.07987900	-0.00644200

45

C	1.25136700	-0.43245200	-0.00001300
C	-0.86748100	-0.97881900	-0.00002800
N	0.47520700	-1.46079300	-0.00004000
C	2.73484600	-0.45906800	0.00000100
H	3.10093800	-1.48774300	-0.00015800
H	3.12208600	0.06877900	-0.88016800
H	3.12205500	0.06848100	0.88036400
C	0.44705100	0.85961400	0.00001800
O	0.85778400	2.01086100	0.00004800
N	-0.85770500	0.42653100	0.00000500
C	-2.03118900	1.28708900	0.00003200
H	-1.68275900	2.32101300	0.00003100

H	-2.63544100	1.11172700	-0.89494100
H	-2.63540700	1.11171600	0.89502600
N	-1.86159100	-1.77517600	-0.00004600
H	-2.75269000	-1.27298200	-0.00003000